

Title

**NITROOXYDERIVATIVES OF CARVEDILOL AND OTHER BETA BLOCKERS
AS ANTIHYPERTENSIVE DRUGS**

5 The present invention relates to β -adrenergic blockers derivatives. More particularly, the present invention relates to β -adrenergic blockers nitrooxyderivatives, pharmaceutical compositions containing them and their use for the treatment of hypertension, cardiovascular diseases, glaucoma, migraine headache, vascular diseases and elevated intraocular pressure.

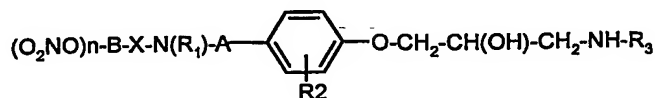
10 β -adrenergic blockers (β -blockers) are widely used in the treatment of hypertension and cardiovascular diseases including angina pectoris, arrhythmias, acute myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure. They work to block the effects of catecholamines at receptor sites in the heart, but they differ somewhat in their ability to block receptors in the blood vessels and lungs. Selective β -blockers have their major actions on the heart, some others are weak stimulators of the β -receptor while still blocking the major actions of catecholamines, some block both the β_1 and β_2 receptors in the heart and those in the blood vessels and have no stimulatory activity and some block other catecholamine receptors that can lead to further vascular effects on blood vessels.

20 Several side effects are associated with this class of drugs such as muscle fatigue, sleep disturbances, decreased heart rate, hypotension, cold extremities, bronchospasm in asthmatic patients, hypoglycemia, increased in plasma lipids. Moreover, abrupt withdrawal after long-term treatment with β -blockers has to be avoided, because an increased sensitivity to β -adrenergic system develops

25 U.S. Pat. No. 6,242,432 discloses derivatives of formula $A-(X_1-NO_2)_{t_0}$ having an antithrombotic activity, wherein A is the residue of a β -adrenergic blocker, X_1 is a bivalent connecting bridge and t_0 is 1 or 2. The invention is limited to particular residues of β -adrenergic blockers.

30 U.S. Pat. No. 5,502,237 and U.S. Pat. No. 5,639,904 disclose derivatives of formula $R_1-Ar-O-CH_2-CH(OH)-CH_2-NH-CH(CH_3)_2$ used for the treatment of cardiovascular affections, wherein R_1 is a chain having at least one nitrooxy group as substituent.

U.S. Pat. No. 4,801,596 discloses aminopropanol derivatives of formula



that can be used for prophylaxis and/or treatment of heart and circulatory diseases, wherein R_3 is an alkyl or a nitrooxyalkyl radical containing 3 to 8 carbon atoms.

It was an object of the present invention to provide new β -adrenergic blockers nitrooxyderivatives having a significantly improved overall pharmacological profile as compared to native β -blockers that are able not only to eliminate or at least reduce the side effects associated with their parent compounds, but also having an improved pharmacological activity and tolerability.

It has been so surprisingly found that the β -adrenergic blockers nitrooxyderivatives of the present invention have a better pharmacological activity and organ protection properties, enhanced effects as anti-inflammatory, and on renal functions. In addition, they are effective in other pathologies including atherosclerosis, diabetes, peripheral vascular diseases (PVD) and elevated intraocular pressure.

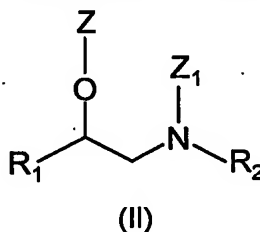
In particular, it has been recognized that the β -adrenergic blockers nitrooxyderivatives of the present invention, differently from the above mentioned compounds of the prior art, exhibit an improved activity on the cardiovascular system and enhanced tolerability and can be employed for treating or preventing hypertension, cardiovascular diseases, glaucoma, migraine headache, vascular diseases and elevated intraocular pressure.

Object of the present invention are β -adrenergic blockers nitrooxyderivatives of general formula (I):



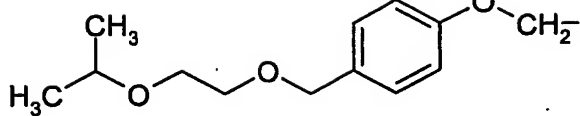
and enantiomers and diastereoisomers and pharmaceutically acceptable salts thereof, wherein s is an integer equal to 1 or 2;

A is selected from the following β -adrenergic blocker residues of formula (II):

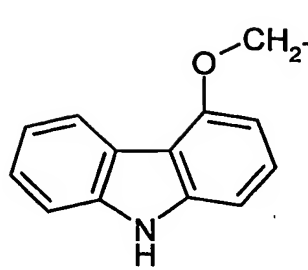


wherein

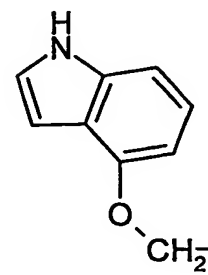
R_1 is selected from the group consisting of:



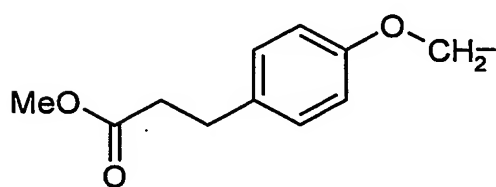
(IIa)



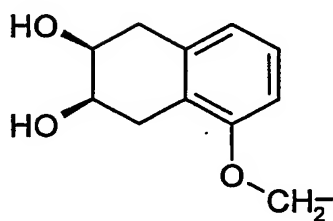
(IIb)



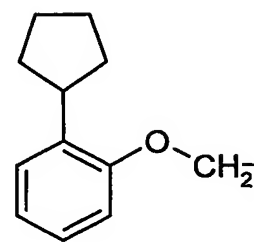
(IIc)



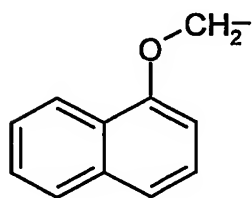
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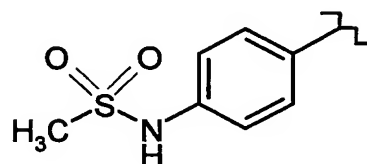
(IIe)



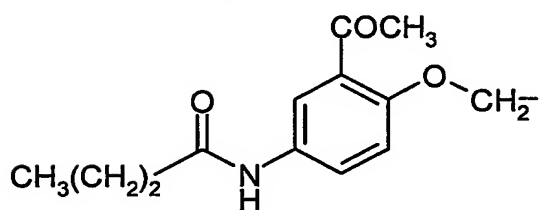
(IIIf)



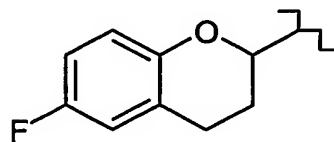
(IIg)



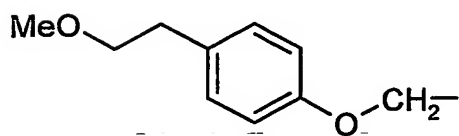
(IIh)



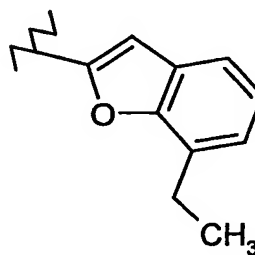
(IIi)



(IIl)

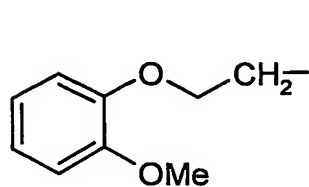


(IIIm)

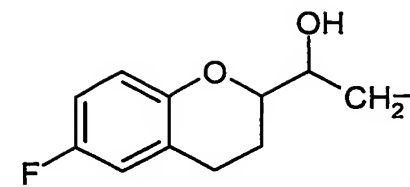


(IIIn)

R₂ is selected from the group consisting of: -CH(CH₃)₂, -C(CH₃)₃ or



(IIIa)



(IIIb)

when the radical R_1 has chosen from the formulae (IIa), (IIc), (IId), (IIg), (IIh), (Ili), (IIIm), R_2 is $-\text{CH}(\text{CH}_3)_2$;

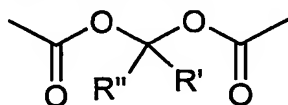
when the radical R_1 has chosen from the formulae (IIe), (IIl) or (IIIn), R_2 is $-\text{C}(\text{CH}_3)_3$;

when R_1 is the radical (IIb), R_2 is (IIIa);

when R_1 is the radical (IIl), R_2 is (IIIb);

Z is H or is a group capable of binding Y selected from the group consisting of:

$-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$ or



wherein R' and R'' are the same or different, and are H or straight or branched C_1 - C_4 alkyl;

Z_1 is H or a $-\text{C}(\text{O})-$ capable of binding Y ;

with the proviso that when s of formula (I) is 1, Z or Z_1 is H;

preferably when s of formula (I) is 2, Z and Z_1 are $-\text{C}(\text{O})-$;

Y is a bivalent radical having the following meanings:

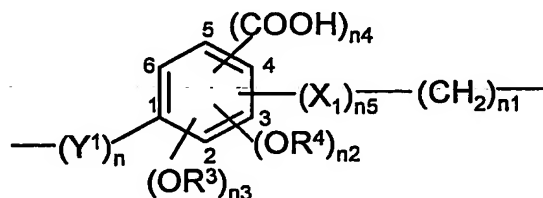
a)

- straight or branched C_1 - C_{20} alkylene, preferably C_1 - C_{10} alkylene, more preferably C_3 - C_6 alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-\text{ONO}_2$ or T , wherein T is $-\text{OC}(\text{O})(\text{C}_1$ - $\text{C}_{10}\text{alkyl})-\text{ONO}_2$, $-\text{O}(\text{C}_1$ - $\text{C}_{10}\text{alkyl})-\text{ONO}_2$;

b)

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1 , wherein T_1 is straight or branched alkyl with from 1 to 10 carbon atoms, T_1 is preferably CH_3 ;

c)



(IV)

wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0 or 1,

5 n₁ is an integer from 1 to 20, preferably from 1 to 10, more preferably n₁ is 1;

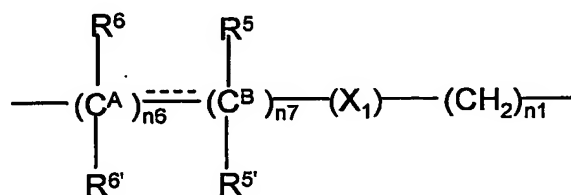
n₂, n₃, n₄ and n₅ are integers equal or different from one another, equal to 0 or 1;

R³ and R⁴ are independently selected from H or CH₃;

Y¹ is -CH₂- or -(CH₂)_{na}-CH=CH- wherein na is an integer from 0 to 20, preferably na is equal to 0;

10 X₁ is -WC(O)- or -C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is oxygen;

d)



(V)

wherein:

15 n₁ is an integer from 1 to 20, preferably from 1 to 10;

X₁ is -WC(O)- or -C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is sulfur or NH,

n₆ is an integer from 1 to 20, preferably from 1 to 5, more preferably n₆ is 1,

n₇ is an integer from 0 to 20, preferably from 0 to 5, more preferably n₇ is 1,

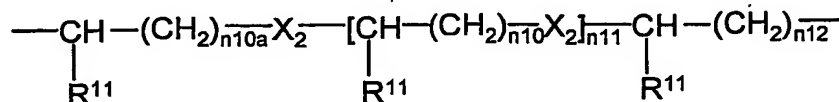
20 R⁵, R^{5'}, R⁶ and R^{6'} are independently selected from the group consisting of: H, CH₃, OH, NH₂, NHCOCH₃, COOH, CH₂SH and C(CH₃)₂SH;

when the bond between the C^A and C^B carbons is a double bond R⁵ and R⁶ or R^{6'} and R^{5'} are absent;

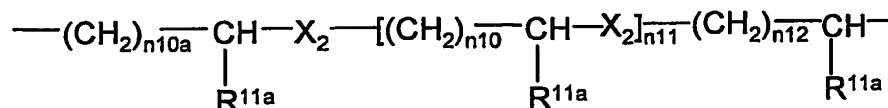
with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d),

25 the -ONO₂ group is linked to the -(CH₂)_{n1}- group;

e)



(VI)



(VII)

wherein X_2 is O or S,

n_{10a} , n_{10} and n_{12} are integer independently selected from 0 to 20,

n_{10a} is preferably selected from 0 to 10, more preferably n_{10a} is 0 or 1,

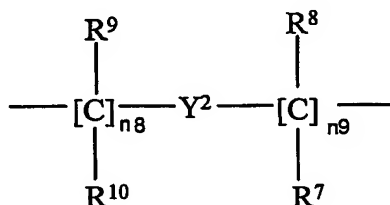
5 n_{10} and n_{12} are preferably selected from 1 to 10, more preferably n_{10} and n_{12} are 1 or 2

n_{11} is an integer from 0 to 6, preferably from 0 to 4, more preferably n_{11} is 0 or 1,

R^{11} is H, CH_3 or nitrooxy group, preferably R^{11} is H or a nitrooxy group and

R^{11a} is CH_3 or nitrooxy group;

f).



10

(VIII)

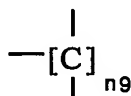
wherein

n_8 is an integer from 0 to 10;

n_9 is an integer from 1 to 10;

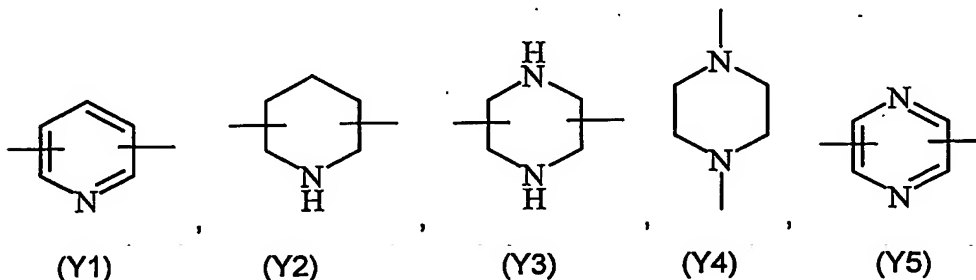
15 R^9 , R^{10} , R^8 , R^7 are same or different, and are H or straight or branched C_1 - C_4 alkyl, preferably R^9 , R^{10} , R^8 , R^7 are H;

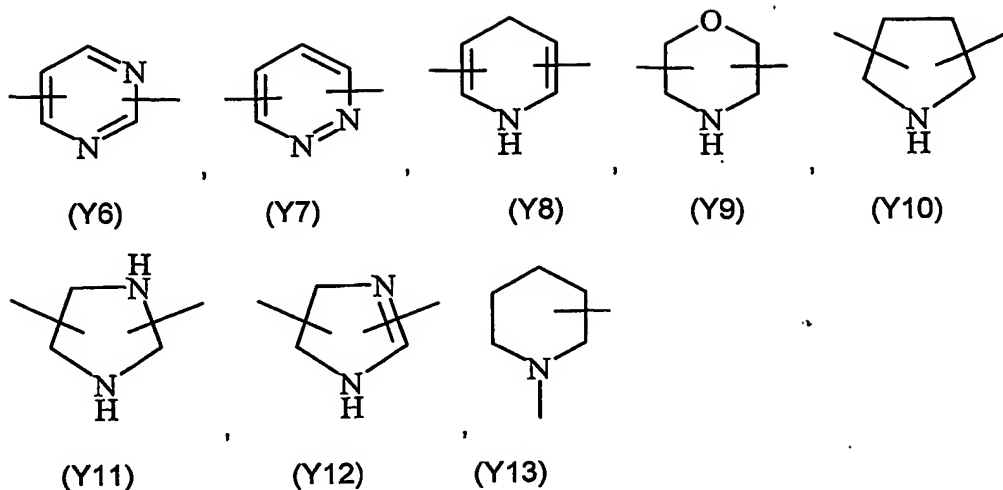
wherein the $-ONO_2$ group is linked to



wherein n_9 is as defined above;

20 Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur, and is selected from the group consisting of

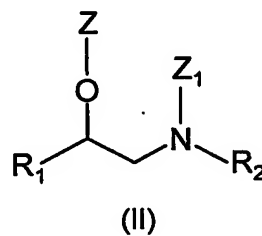




5 One embodiment provides compounds of formula (I) wherein:

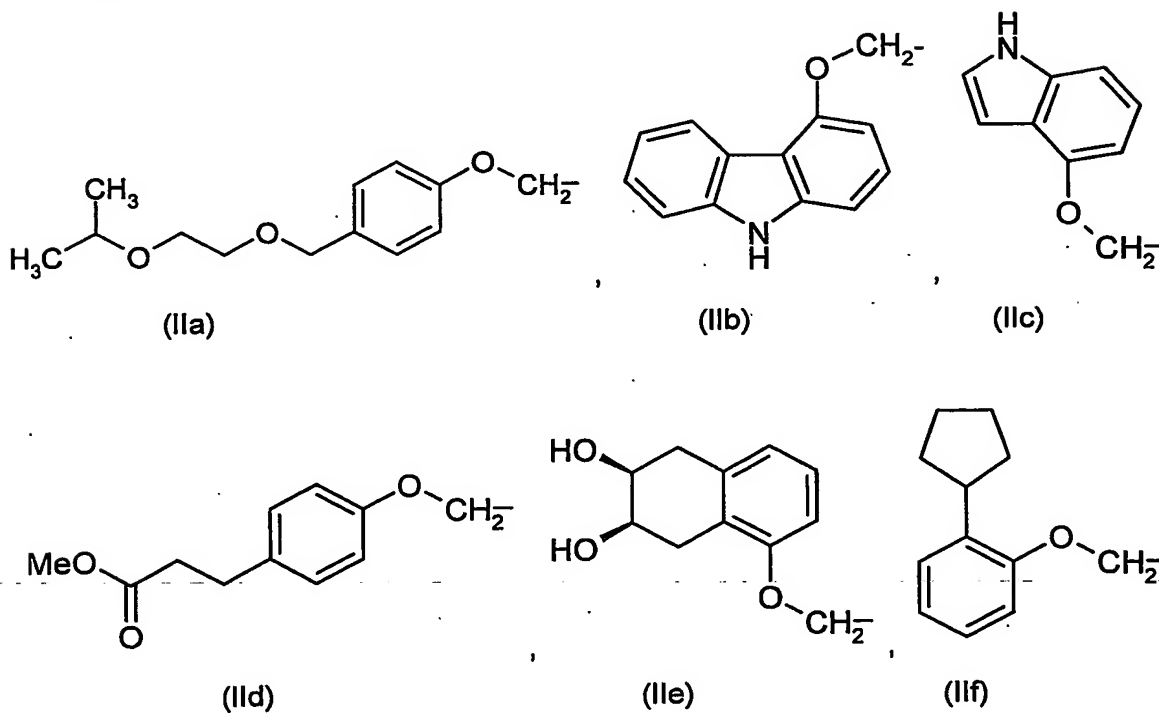
s is 2,

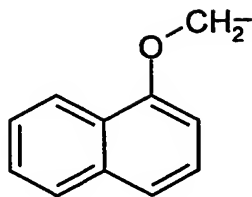
A is selected from the following β -adrenergic blocker residues of formula (II):



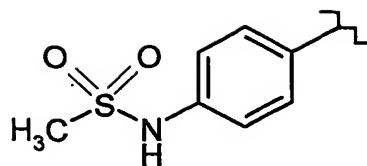
10 wherein

R_1 is selected from the group consisting of:

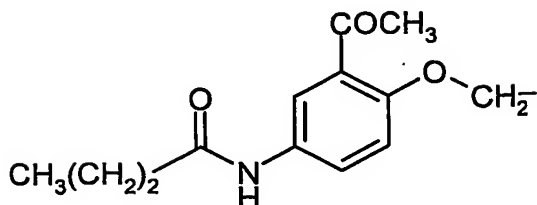




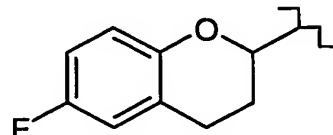
(IIg)



(IIh)

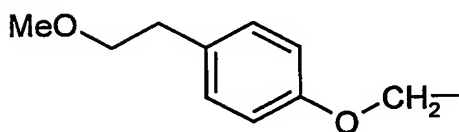


(Ili)

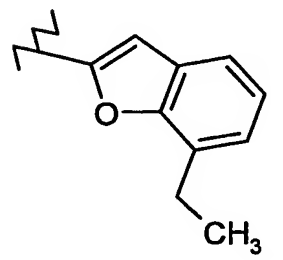


(III)

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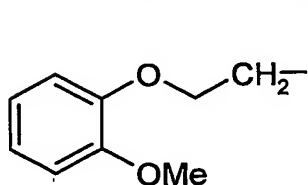


(IIIm)

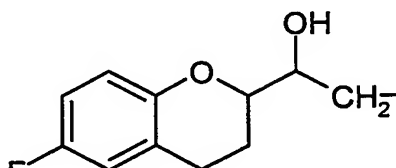


(IIIn)

R_2 is selected from the group consisting of: $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$ or



(IIIa)



(IIIb)

10

when the radical R_1 has chosen from the formulae (IIa), (IIc), (IId), (IIg), (IIh), (Ili), (IIIm), R_2 is $-\text{CH}(\text{CH}_3)_2$;

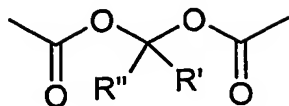
when the radical R_1 has chosen from the formulae (Ile), (IIl) or (IIIn), R_2 is $-\text{C}(\text{CH}_3)_3$;

15 when R_1 is the radical (IIb), R_2 is (IIIa);

when R_1 is the radical (IIl), R_2 is (IIIb);

Z is a group capable of binding Y selected from the group consisting of:

$-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$ or



wherein R' and R'' are the same or different, and are H or straight or branched C₁-C₄ alkyl;
 Z₁ is H or a -C(O)- capable of binding Y, preferably Z and Z₁ are -C(O)-;
 Y is a bivalent radical having the following meaning:

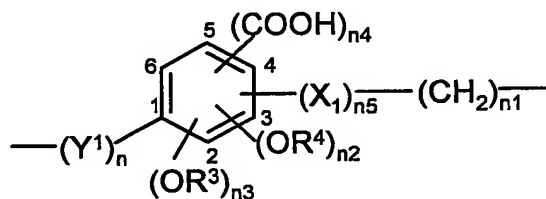
5 a)

- straight or branched C₁-C₂₀ alkylene, preferably C₁-C₁₀ alkylene, more preferably C₃-C₆ alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, -ONO₂ or T, wherein T is -OC(O)(C₁-C₁₀alkyl)-ONO₂, -O(C₁-C₁₀alkyl)-ONO₂;

10 b)

- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T₁, wherein T₁ is straight or branched alkyl with from 1 to 10 carbon atoms, T₁ is preferably CH₃;

c)



15

(IV)

wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0 or 1,

20 n₁ is an integer from 1 to 20, preferably from 1 to 10, more preferably n₁ is 1;

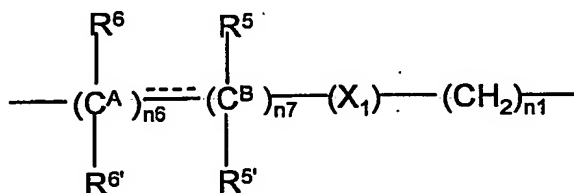
n₂, n₃, n₄ and n₅ are integers equal or different from one another, equal to 0 or 1;

R³ and R⁴ are independently selected from H or CH₃;

Y¹ is -CH₂- or -(CH₂)_{na}-CH=CH- wherein na is an integer from 0 to 20, preferably na is equal to 0;

25 X₁ is -WC(O)- or -C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is oxygen;

d)



10

(V)

wherein:

n₁ is an integer from 1 to 20, preferably from 1 to 10;

X₁ is -WC(O)- or -C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is sulfur or

5 NH;

n₆ is an integer from 1 to 20, preferably from 1 to 5, more preferably n₆ is 1,

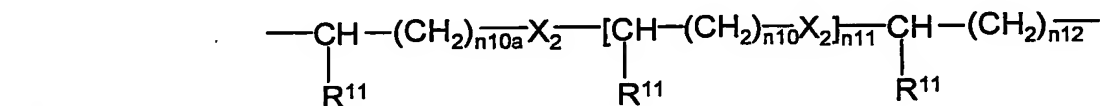
n₇ is an integer from 0 to 20, preferably from 0 to 5, more preferably n₇ is 1,

R⁵ and R^{5'} R⁶ and R^{6'} are independently selected from the group consisting of: H, CH₃, OH, NH₂, NHCOCH₃, COOH, CH₂SH and C(CH₃)₂SH;

10 when the bond between the C^A and C^B carbons is a double bond R⁵ and R⁶ or R^{6'} and R^{5'} are absent;

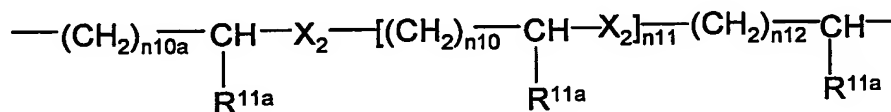
with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the -ONO₂ group is linked to the -(CH₂)_{n₁}- group;

e)



15

(VI)



(VII)

wherein X₂ is O or S,

20 n_{10a}, n₁₀ and n₁₂ are integer independently selected from 0 to 20,

n_{10a} is preferably selected from 0 to 10, more preferably n_{10a} is 0 or 1;

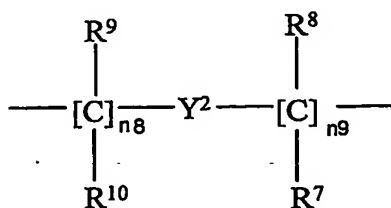
n₁₀ and n₁₂ are preferably selected from 1 to 10, more preferably n₁₀ and n₁₂ are 1 or 2;

n₁₁ is an integer from 0 to 6, preferably from 0 to 4, more preferably n₁₁ is 0 or 1;

R¹¹ is H, CH₃ or nitrooxy group, preferably R¹¹ is H or nitroxy;

25 R^{11a} is CH₃ or nitrooxy group;

f)



(VIII)

wherein

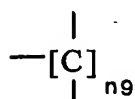
n8 is an integer from 0 to 10;

n9 is an integer from 1 to 10;

R⁹, R¹⁰, R⁸, R⁷ are same or different, and are H or straight or branched C₁-C₄ alkyl,

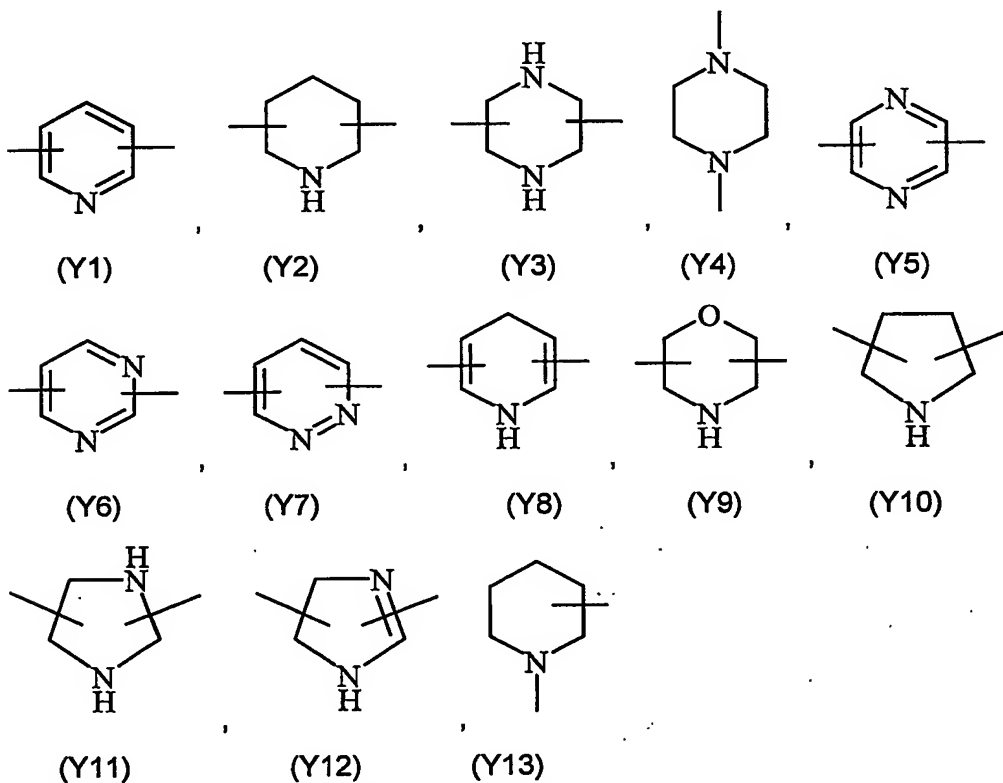
5 preferably R⁹, R¹⁰, R⁸, R⁷ are H;

wherein the -ONO₂ group is linked to



wherein n9 is as defined above;

Y² is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing
 10 one or more heteroatoms selected from nitrogen, oxygen, sulfur,
 and is selected from the group consisting of

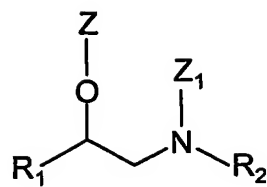


Another embodiment provides compounds of formula (I) wherein:

s is 1,

20 A is selected from the following β -adrenergic blocker residues of formula (II):

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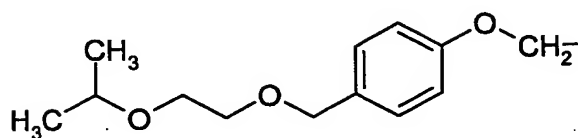


(II)

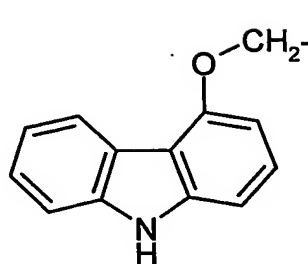
wherein

 R_1 is selected from the group consisting of:

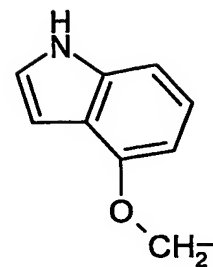
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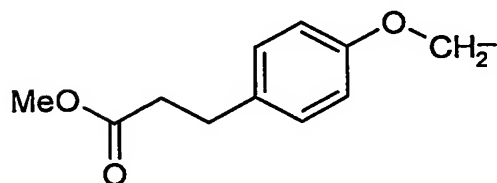
(IIa)



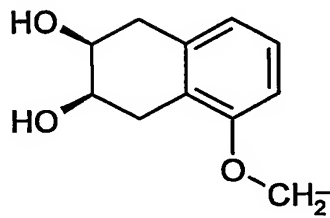
(IIb)



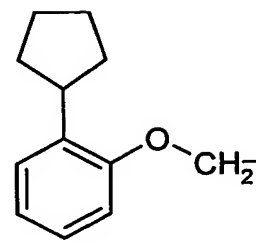
(IIc)



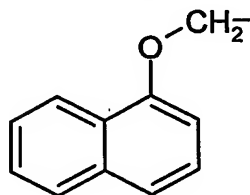
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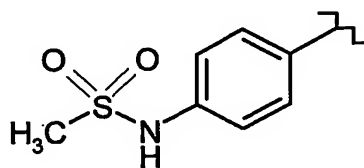
(IIe)



(IIIf)

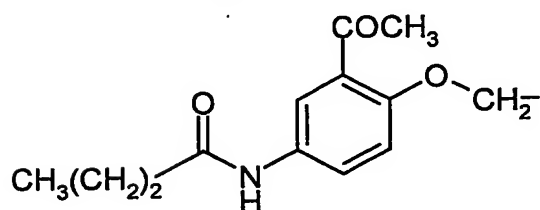


(IIg)

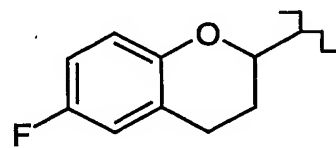


(IIh)

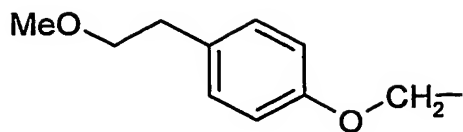
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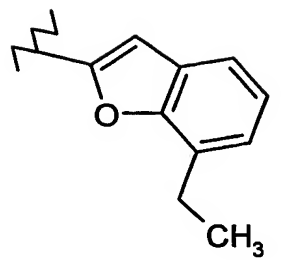
(III)



(IIL)

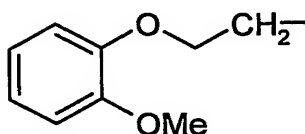


(IIIm)

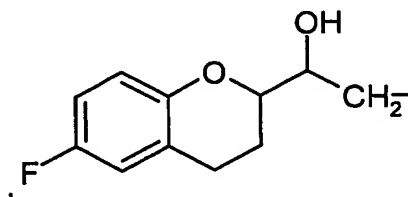


(IIIn)

R_2 is selected from the group consisting of: $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$ or



(IIIa)



(IIIb)

5

when the radical R_1 has chosen from the formulae (IIa), (IIc), (IId), (IIg), (IIh), (Ili), (IIm), R_2 is $-\text{CH}(\text{CH}_3)_2$;

when the radical R_1 has chosen from the formulae (IIe), (IIf) or (IIIn), R_2 is $-\text{C}(\text{CH}_3)_3$;

10 when R_1 is the radical (IIb), R_2 is (IIIa);

when R_1 is the radical (IIL), R_2 is (IIIb);

Z is H and Z_1 a $-\text{C}(\text{O})-$ capable of binding Y;

Y is a bivalent radical having the following meaning:

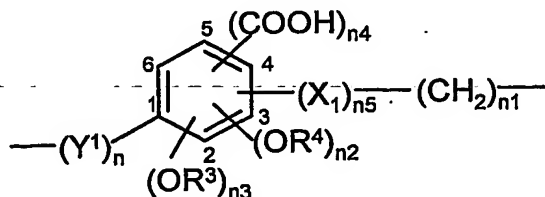
a)

15 - straight or branched C_1 - C_{20} alkylene, preferably C_1 - C_{10} alkylene, more preferably C_3 - C_6 alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-\text{ONO}_2$ or T, wherein T is $-\text{OC}(\text{O})(\text{C}_1$ - $\text{C}_{10}\text{alkyl})-\text{ONO}_2$, $-\text{O}(\text{C}_1$ - $\text{C}_{10}\text{alkyl})-\text{ONO}_2$;

b)

20 - cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1 , wherein T_1 is straight or branched alkyl with from 1 to 10 carbon atoms, T_1 is preferably CH_3 ;

c)



(IV)

wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0 or 1, and n1 is an integer from 1 to 20, preferably from 1 to 10, more preferably n1 is 1;

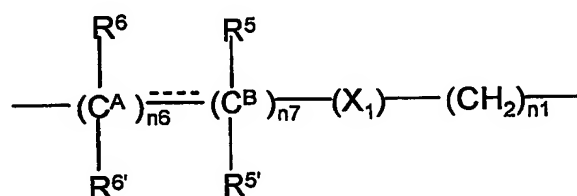
5 n2, n3, n4 and n5 are integers equal or different from one another, equal to 0 or 1;

R³ and R⁴ are independently selected from H or CH₃;

Y¹ is -CH₂- or -(CH₂)_{na}-CH=CH- wherein na is an integer from 0 to 20, preferably na is equal to 0;

X₁ is -WC(O)- or -C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is oxygen;

10 d)



(V)

wherein:

n1 is an integer from 1 to 20, preferably from 1 to 10;

15 X₁ is -WC(O)- or -C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is sulfur or NH;

n6 is an integer from 1 to 20, preferably from 1 to 5, more preferably n6 is 1,

n7 is an integer from 0 to 20, preferably from 0 to 5, more preferably n7 is 1,

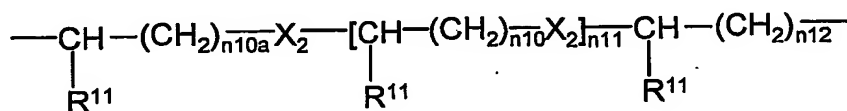
R⁵ and R^{5'} R⁶ and R^{6'} are independently selected from the group consisting of: H, CH₃, OH,

20 NH₂, NHCOCH₃, COOH, CH₂SH and C(CH₃)₂SH;

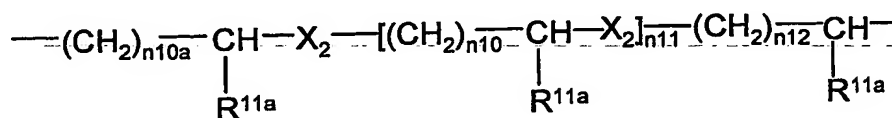
when the bond between the C^A and C^B carbons is a double bond R⁵ and R⁶ or R^{6'} and R^{5'} are absent;

with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the -ONO₂ group is linked to a -(CH₂)_{n1}- group;

25 e)



(VI)



(VII)

wherein X_2 is O or S,

n_{10a} , n_{10} and n_{12} are integer independently selected from 0 to 20,

n_{10a} is preferably selected from 0 to 10, more preferably n_{10a} is 0 or 1;

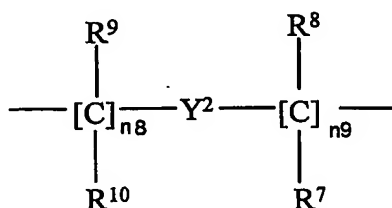
n_{10} and n_{12} are preferably selected from 1 to 10, more preferably n_{10} and n_{12} are 1 or 2;

5 n_{11} is an integer from 0 to 6, preferably from 0 to 4, more preferably n_{11} is 0 or 1;

R^{11} is H, CH_3 or nitrooxy group, preferably R^{11} is H or nitroxy;

R^{11a} is CH_3 or nitrooxy group;

f)



(VIII)

wherein

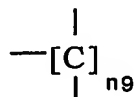
n_8 is an integer from 0 to 10;

n_9 is an integer from 1 to 10;

R^9 , R^{10} , R^8 , R^7 are same or different, and are H or straight or branched C_1 - C_4 alkyl,

15 preferably R^9 , R^{10} , R^8 , R^7 are H;

wherein the $-ONO_2$ group is linked to

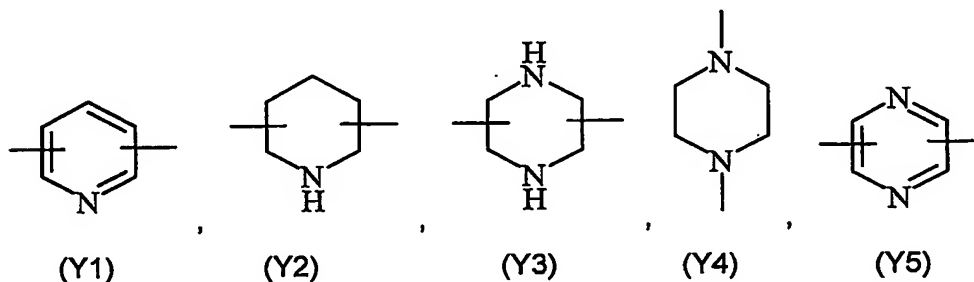


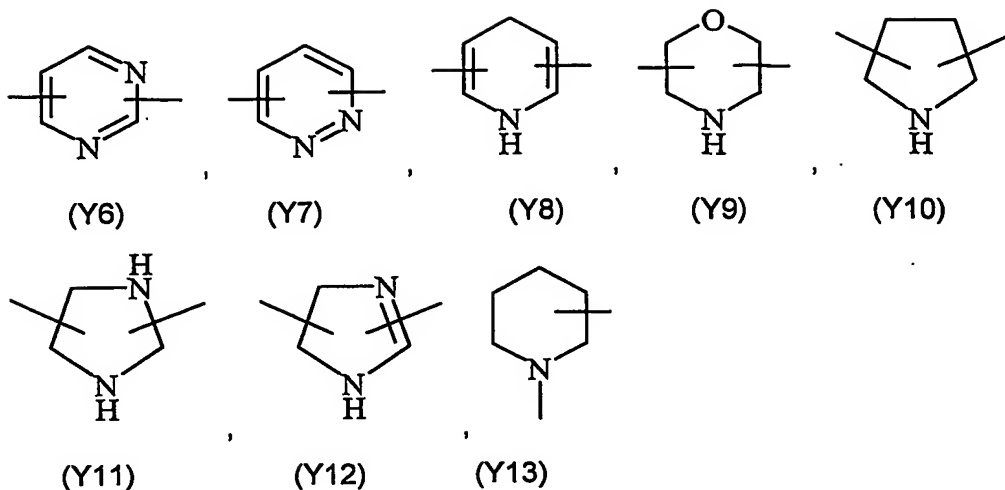
wherein n_9 is as defined above;

Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing

20 one or more heteroatoms selected from nitrogen, oxygen, sulfur,

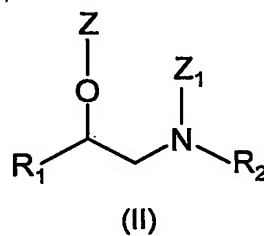
and is selected from the group consisting of





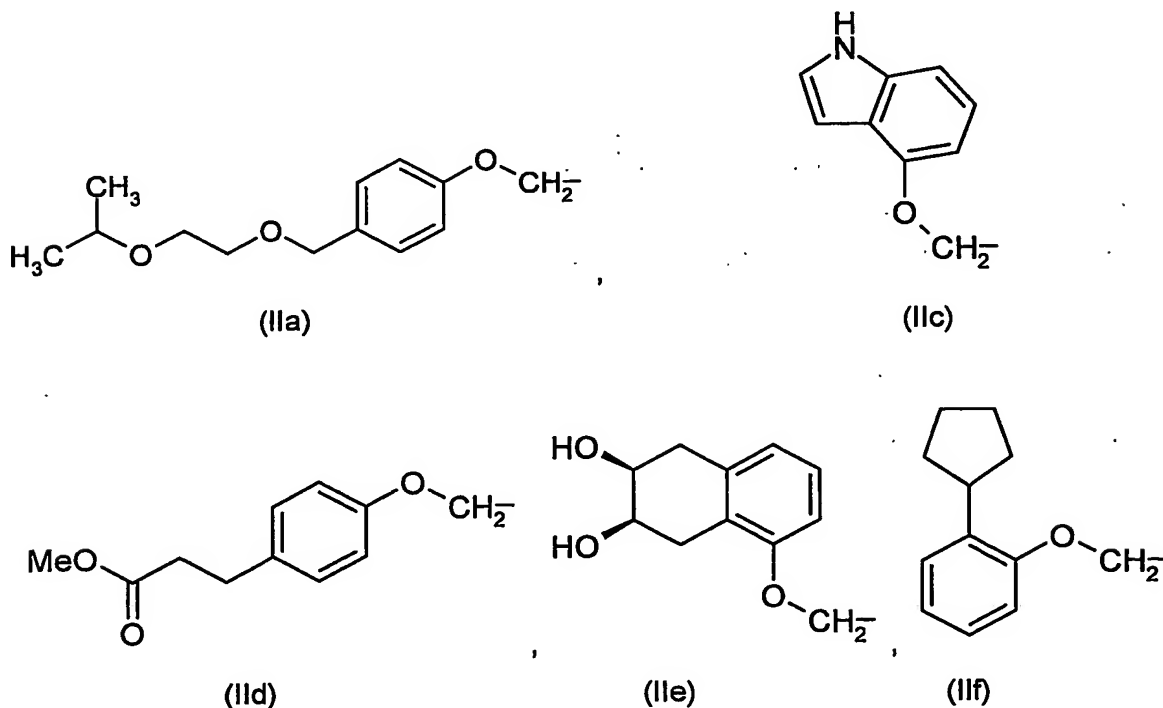
- 5 Another embodiment provides compounds of formula (I) wherein s is 1,

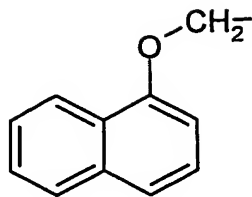
A is selected from the following β -adrenergic blocker residues of formula (II):



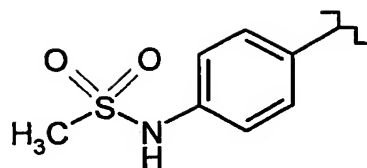
- 10 wherein

R_1 is selected from the group consisting of:

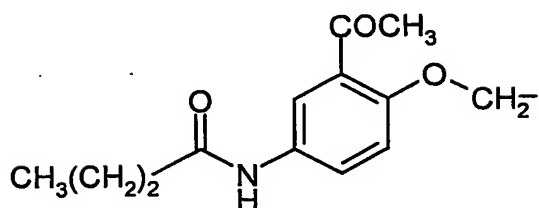




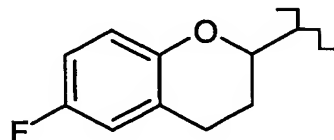
(IIg)



(IIh)

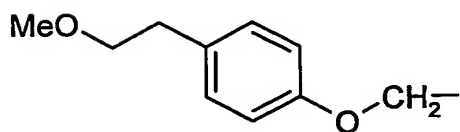


(III)

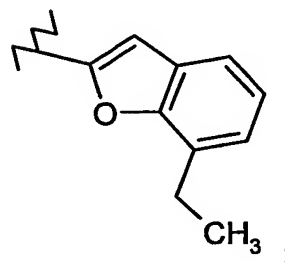


(IIIa)

5

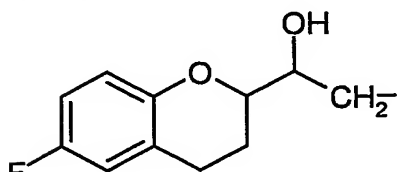


(IIIm)



(IIIn)

R_2 is selected from the group consisting of: $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$ or



(IIIb)

10

when the radical R_1 has chosen from the formulae (IIa), (IIc), (IIe), (IIg), (IIh), (IIi), (IIm), R_2 is $-\text{CH}(\text{CH}_3)_2$;

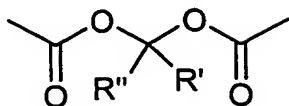
when the radical R_1 has chosen from the formulae (IIf), (IIl) or (IIIn), R_2 is $-\text{C}(\text{CH}_3)_3$;

15 when R_1 is the radical (III), R_2 is (IIIb);

Z_1 is H;

Z is a group capable of binding Y selected from the group consisting of:

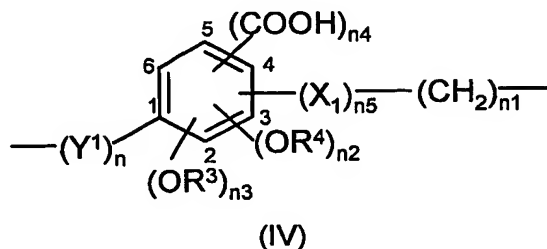
$-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$ or



wherein R' and R'' are the same or different, and are H or straight or branched C₁-C₄ alkyl;

Y is a bivalent radical having the following meaning:

c)



5

wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0 or 1,

10 n₁ is an integer from 1 to 20, preferably from 1 to 10; more preferably n₁ is 1;

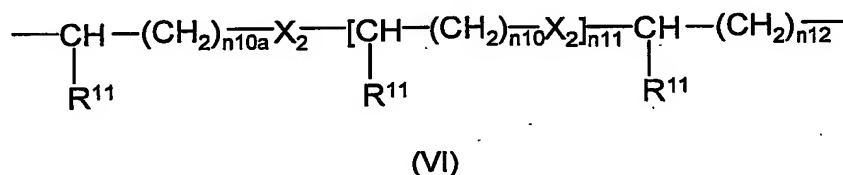
n₂, n₃, n₄ and n₅ are integers equal or different from one another, equal to 0 or 1;

R³ and R⁴ are independently selected from H or CH₃;

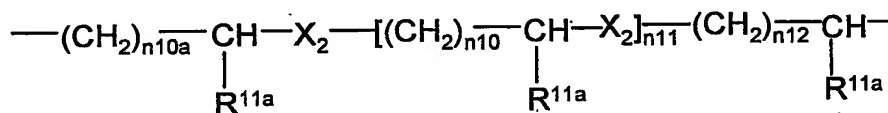
Y¹ is -CH₂- or -(CH₂)_{na}-CH=CH- wherein na is an integer from 0 to 20, preferably na is equal to 0;

15 X₁ is -WC(O)- or -C(O)W-, wherein W is oxygen, sulfur or NH, preferably W is oxygen;

e)



(VI)



(VII)

20

wherein

X₂ is O or S,

n_{10a} is 0 or 1,

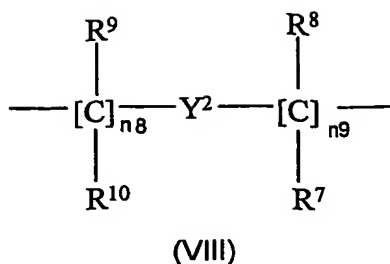
n₁₁ is 0 or 1,

25 n₁₀ and n₁₂ are 1 or 2;

R¹¹ is H, CH₃ or nitrooxy group;

R^{11a} is CH₃ or nitrooxy group;

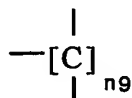
f)



wherein

5 n_8 is an integer from 0 to 10; n_9 is an integer from 1 to 10;

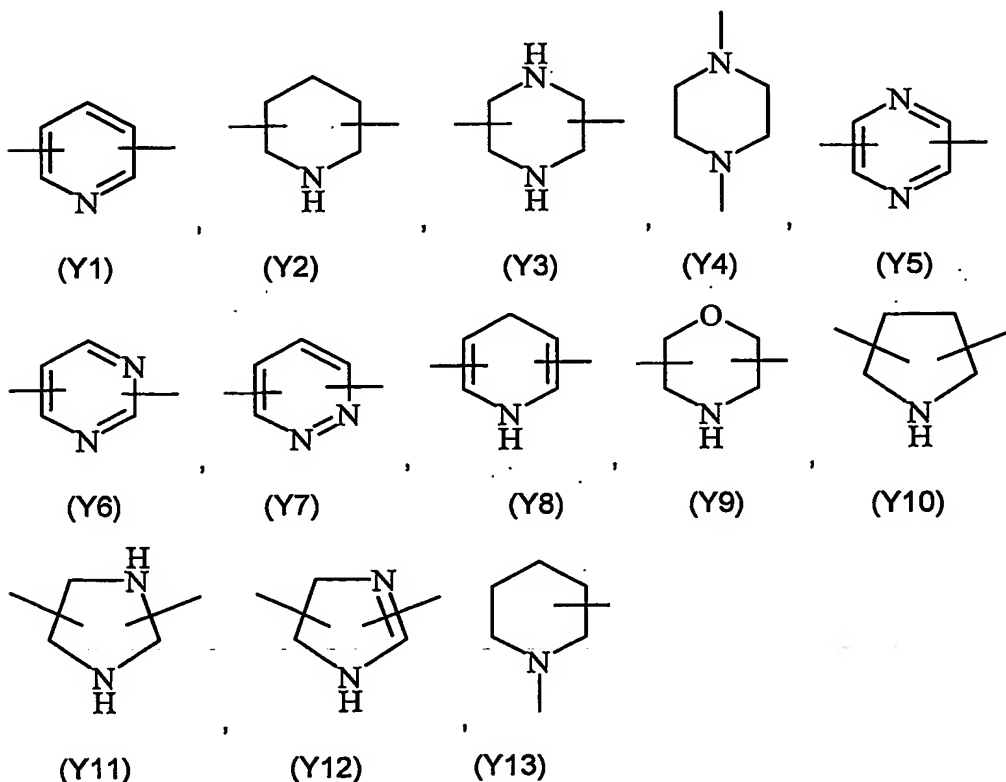
R^9 , R^{10} , R^8 , R^7 are same or different, and are H or straight or branched $\text{C}_1\text{-C}_4$ alkyl, preferably R^9 , R^{10} , R^8 , R^7 are H;

wherein the -ONO_2 group is linked to

10

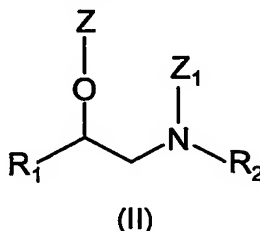
wherein n_9 is as defined above;

Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur, and is selected from the group consisting of



Another embodiment provides compounds of formula (I) wherein s is an integer equal to 1 or 2

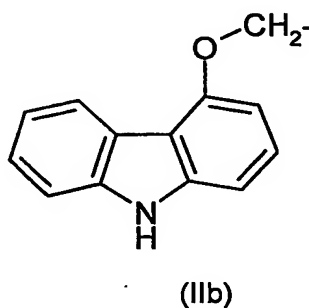
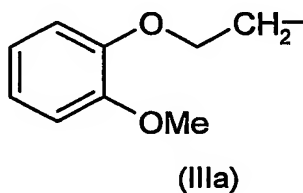
A is the β -adrenergic blocker residue of formula (II):



5

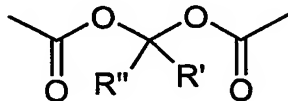
wherein

R₁ is (IIb)

10 R₂ is (IIIa)

Z is H or is a group capable of binding Y selected from the group consisting of:

-C(O)-, -C(O)O- or



15

wherein R' and R'' are the same or different, and are H or straight or branched C₁-C₄ alkyl;

Z₁ is H or a -C(O)- capable of binding Y;

with the proviso that when s of formula (I) is 1, Z or Z₁ is H;

preferably when s of formula (I) is 2, Z and Z₁ are -C(O)-;

20 Y is a bivalent radical having the following meaning:

a)

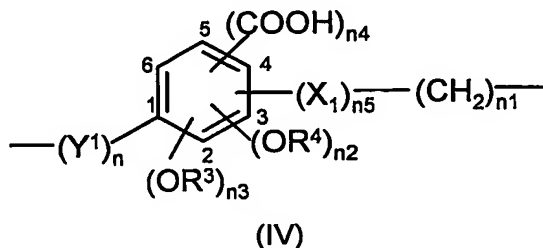
--straight or branched-C₁-C₂₀ alkylene, preferably C₁-C₁₀ alkylene, more preferably C₃-C₆ alkylene, being optionally substituted with one or more of the substituents selected from

the group consisting of: halogen atoms, hydroxy, $-\text{ONO}_2$ or T, wherein T is $-\text{OC}(\text{O})(\text{C}_1\text{-C}_{10}\text{alkyl})-\text{ONO}_2$, $-\text{O}(\text{C}_1\text{-C}_{10}\text{alkyl})-\text{ONO}_2$;

b)

- 5 - cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T_1 , wherein T_1 is straight or branched alkyl with from 1 to 10 carbon atoms, T_1 is preferably CH_3 ;

c)



- 10 wherein:

n is an integer from 0 to 20, preferably n is an integer from 0 to 10, more preferably n is 0 or 1,

n_1 is an integer from 1 to 20, preferably from 1 to 10, more preferably n_1 is 1,

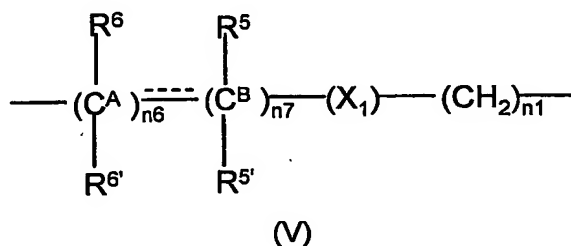
n_2 , n_3 , n_4 and n_5 are integers equal or different from one another, equal to 0 or 1,

- 15 R^3 and R^4 are independently selected from H or CH_3 ;

Y^1 is $-\text{CH}_2-$ or $-(\text{CH}_2)_{n_a}-\text{CH}=\text{CH}-$ wherein n_a is an integer from 0 to 20, preferably n_a is equal to 0;

X_1 is $-\text{WC}(\text{O})-$ or $-\text{C}(\text{O})\text{W}-$, wherein W is oxygen, sulfur or NH, preferably W is oxygen;

d)



- 20

wherein:

n_1 is an integer from 1 to 20, preferably from 1 to 10;

X_1 is $-\text{WC}(\text{O})-$ or $-\text{C}(\text{O})\text{W}-$, wherein W is oxygen, sulfur or NH, preferably W is sulfur or NH;

- 25

n_6 is an integer from 1 to 20, preferably from 1 to 5, more preferably n_6 is 1,

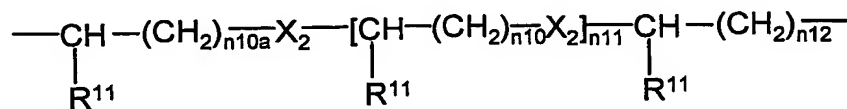
n_7 is an integer from 0 to 20, preferably from 0 to 5, more preferably n_7 is 1,

R^5 and $\text{R}^{5'}$, R^6 and $\text{R}^{6'}$ are independently selected from the group consisting of: H, CH_3 , OH, NH_2 , NHCOCH_3 , COOH , CH_2SH and $\text{C}(\text{CH}_3)_2\text{SH}$;

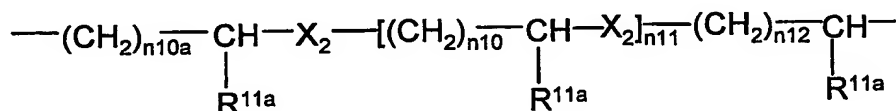
when the bond between the C^A and C^B carbons is a double bond R⁵ and R⁶ or R^{6'} and R^{5'} are absent;

with the proviso that when Y is selected from the bivalent radicals mentioned under c)-d), the -ONO₂ group is linked to a -(CH₂)_{n1}- group;

5 e)



(VI)



(VII)

10 wherein X₂ is O or S, n10a, n10 and n12 are integer independently selected from 0 to 20, n10a is preferably selected from 0 to 10, more preferably n10a is 0 or 1;

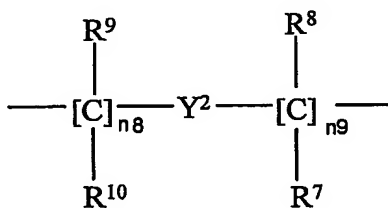
n10 and n12 are preferably selected from 1 to 10, more preferably n10 and n12 are 1 or 2,

n11 is an integer from 0 to 6, preferably from 0 to 4, more preferably n11 is 0 or 1;

R¹¹ is H, CH₃ or nitrooxy group, preferably R¹¹ is H or a nitrooxy group,

15 R^{11a} is CH₃ or nitrooxy group;

f)



(VIII)

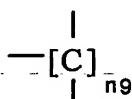
wherein

20 n8 is an integer from 0 to 10;

n9 is an integer from 1 to 10;

R⁹, R¹⁰, R⁸, R⁷ are same or different, and are H or straight or branched C₁-C₄ alkyl, preferably R⁹, R¹⁰, R⁸, R⁷ are H;

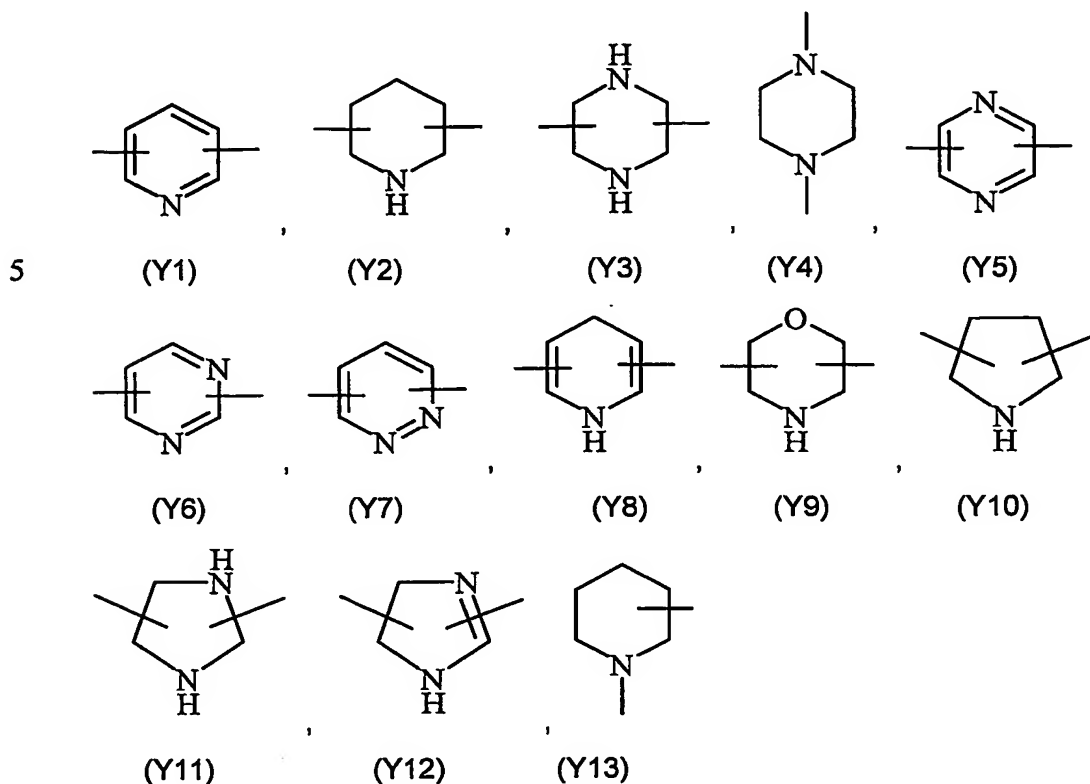
wherein the -ONO₂ group is linked to



25

wherein n9 is as defined above;

Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur, and is selected from the group consisting of



10

Preferred compounds are those of formula (I) wherein:

s is 2,

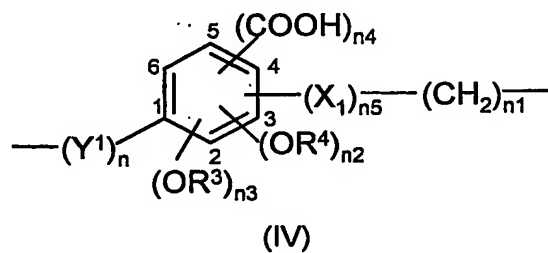
A is a β -adrenergic blocker residues of formula (II) as above defined

Z and Z_1 are $-(CO)-$

15 Y is a bivalent radical having the following meanings:

a) straight C_1 - C_{10} alkylene, preferably C_3 - C_6 alkylene;

c)



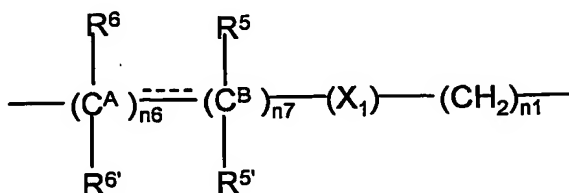
20 wherein the $-ONO_2$ group is bound to $(CH_2)_{n1}$;

n, n2, n3, n4, n5 are equal to 0, n1 is 1 and the $-(CH_2)_{n1}-$ group is bound to the phenyl ring through the $[C]_2$ or $[C]_3$ or $[C]_4$;

or n_1, n_2, n_5 are 1, n_3 and n_4 are equal to 0, and n_1 is an integer from 1 to 10,

Y^1 is $-(CH_2)_{n_a}-CH=CH-$ wherein n_a is 0, X_1 is $-WC(O)-$ wherein W is oxygen and the $WC(O)$ group is bound to the phenyl ring through the $[C]_4$, R^4 is CH_3 and the (OR^4) group is bound to the phenyl ring through the $[C]_3$;

d)



(V)

wherein

10 n_1 is an integer from 1 to 10,

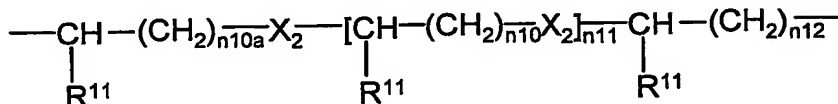
n_6 and n_7 are 1,

X_1 is $-WC(O)-$ wherein W is sulfur,

$R^5, R^{5'}$ and $R^{6'}$ are H, R^6 is $NHCOCH_3$ and

the $-ONO_2$ is bound to the $-(CH_2)_{n_1}-$ group;

15 e)



(VI)

wherein

X_2 is O or S, and n_{11} is 0,

20 n_{10a} is an integer from 0 to 10,

n_{12} is an integer from 1 to 10,

R^{11} is H or a nitrooxy group

and the $-ONO_2$ group is bound to $(CH_2)_{n_{12}}$;

Another group of preferred compounds comprises compounds of formula (I)

25 wherein

s is 1,

A is a β -adrenergic blocker residues of formula (II) as above defined,

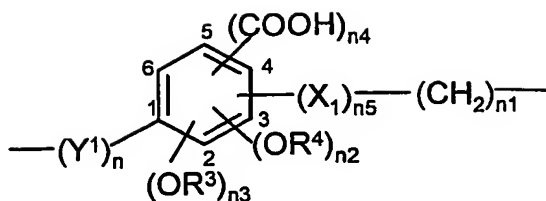
Z is H,

Z_1 is $-(CO)-$

30 Y is a bivalent radical having the following meanings:

a) straight C_1 - C_{10} alkylene, preferably C_3 - C_8 alkylene;

c)



(IV)

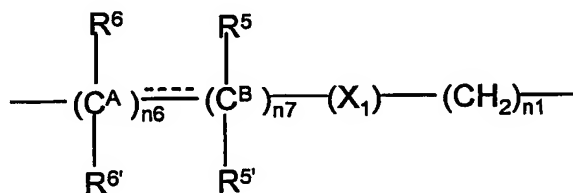
wherein the $-\text{ONO}_2$ group is bound to $(\text{CH}_2)_{n1}$;

5 $n, n2, n3, n4, n5$ are equal to 0, $n1$ is 1 and the $-(\text{CH}_2)_{n1}-$ group is bound to the phenyl ring through the $[\text{C}]_2$ or $[\text{C}]_3$ or $[\text{C}]_4$;

or $n, n2, n5$ are 1, $n3$ and $n4$ are equal to 0, and $n1$ is an integer from 1 to 10, Y^1 is $-(\text{CH}_2)_{na}-\text{CH}=\text{CH}-$ wherein na is 0, X_1 is $-\text{WC}(\text{O})-$ wherein W is oxygen and the $\text{WC}(\text{O})$ group is bound to the phenyl ring through the $[\text{C}]_4$, R^4 is CH_3 and the (OR^4) group is bound

10 to the phenyl ring through the $[\text{C}]_3$;

d)



(V)

wherein

15 $n1$ is an integer from 1 to 10;

X_1 is $-\text{WC}(\text{O})-$ wherein W is sulfur;

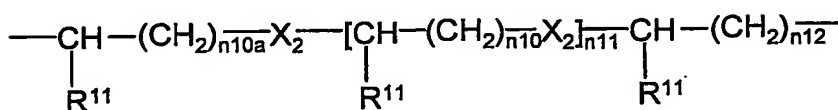
$n6$ is 1

$n7$ is 1,

$\text{R}^6, \text{R}^{6'}, \text{R}^{6''}$ are H, R^6 is, NHCOCH_3 and

20 the $-\text{ONO}_2$ is bound to the $-(\text{CH}_2)_{n1}-$ group;

e)



(VI)

wherein

25 X_2 is O or S, and $n11$ is 0;

$n10a$ is an integer from 0 to 10,

$n12$ is an integer from 1 to 10,

R^{11} is H or a nitrooxy group

and the $-\text{ONO}_2$ group is bound to $(\text{CH}_2)_{n12}$;

Another group of preferred compounds comprises compounds of formula (I)

wherein

5 s is 1,

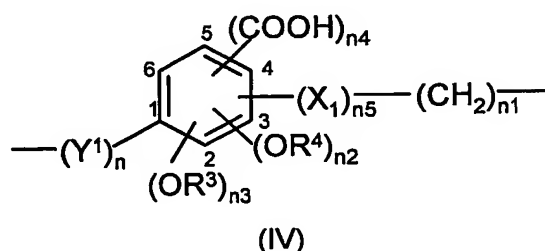
A is a β -adrenergic blocker residues of formula (II) as above defined,

Z_1 is H,

Z is $-(\text{CO})-$ or $-\text{C}(\text{O})\text{O}-$ and

Y is a bivalent radical having the following meanings:

10 c)



wherein the $-\text{ONO}_2$ group is bound to $(\text{CH}_2)_{n1}$;

$n, n2, n3, n4, n5$ are equal to 0,

15 $n1$ is 1 and the $-(\text{CH}_2)_{n1}-$ group is bound to the phenyl ring through the $[\text{C}]_2$ or $[\text{C}]_3$ or $[\text{C}]_4$;
or in formula (IV)

$n, n2, n5$ are 1,

$n3$ and $n4$ are equal to 0,

$n1$ is an integer from 1 to 10,

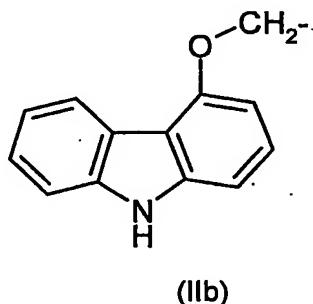
20 Y^1 is $-(\text{CH}_2)_{na}-\text{CH}=\text{CH}-$ wherein na is 0, X_1 is $-\text{WC}(\text{O})-$ wherein W is oxygen and the $\text{WC}(\text{O})$ group is bound to the phenyl ring through the $[\text{C}]_4$, R^4 is CH_3 and the (OR^4) group is bound to the phenyl ring through the $[\text{C}]_3$;

Another groups of preferred compounds comprises compounds of formula (I) wherein:

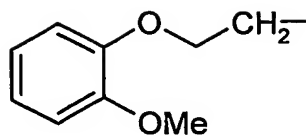
s is 1,

25 A is the β -adrenergic blocker residues of formula (II) wherein

R_1 is



R₂ is



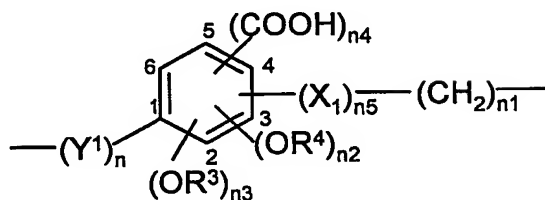
(IIIa)

Z₁ is H and Z is $-(CO)-$ or $-C(O)O-$ and

5 Y is a bivalent radical having the following meanings:

a) straight C₁-C₁₀ alkylene, preferably C₃-C₆ alkylene;

c)



(IV)

10 wherein the $-ONO_2$ group is bound to $(CH_2)_{n1}$;

n, n₂, n₃, n₄, n₅ are equal to 0, n₁ is 1 and the $-(CH_2)_{n1}-$ group is bound to the phenyl ring through the [C]₂ or [C]₃ or [C]₄;

or in formula (IV)

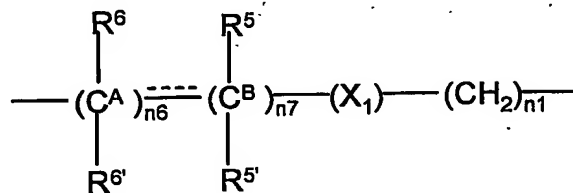
n, n₂, n₅ are 1, n₃ and n₄ are equal to 0,

15 n₁ is an integer from 1 to 10,

Y¹ is $-(CH_2)_{na}-CH=CH-$ wherein n_a is 0,

X₁ is $-WC(O)-$ wherein W is oxygen and the WC(O) group is bound to the phenyl ring through the [C]₄, R⁴ is CH₃ and the (OR⁴) group is bound to the phenyl ring through the [C]₃;

20 d)



(V)

wherein

n₁ is an integer from 1 to 10,

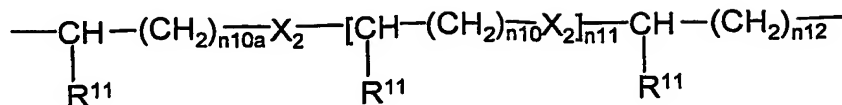
25 n₆ and n₇ are 1,

X₁ is $-WC(O)-$ wherein W is sulfur,

R⁵, R^{5'} and R^{6'} are H, R⁶ is NHCOCH₃ and

the $-\text{ONO}_2$ is bound to the $-(\text{CH}_2)_{n1}-$ group;

e)



(VI)

5 wherein

X_2 is O or S, and $n11$ is 0,

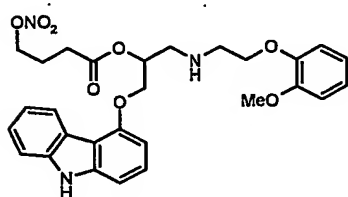
$n10a$ is an integer from 0 to 10,

$n12$ is an integer from 1 to 10,

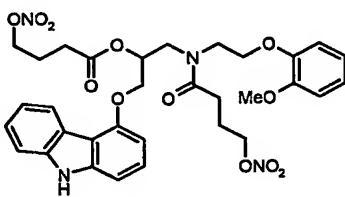
R^{11} is H or a nitrooxy group

10 and the $-\text{ONO}_2$ group is bound to $(\text{CH}_2)_{n12}$.

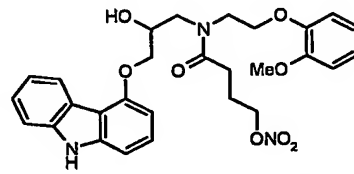
Most preferred compounds of formula (I) according to the present invention are the following:



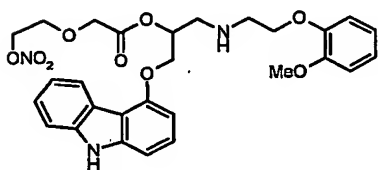
(1)



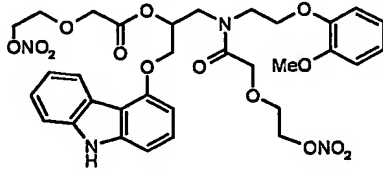
(2)



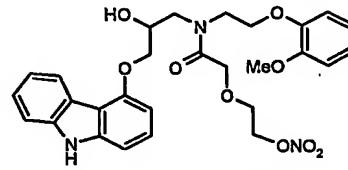
(3)



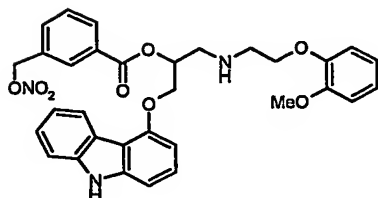
(4)



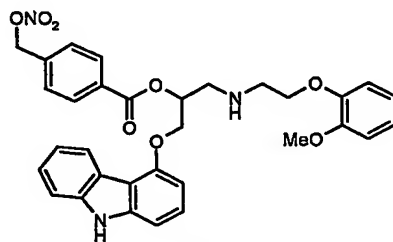
(5)



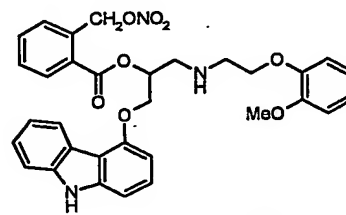
(6)



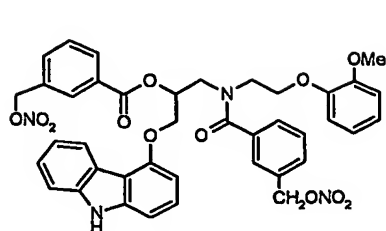
(7)



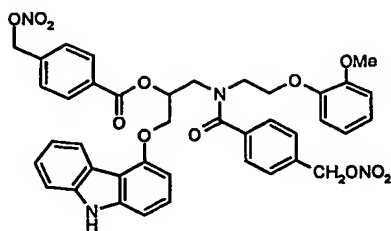
(8)



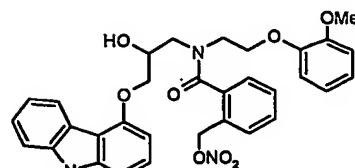
(9)



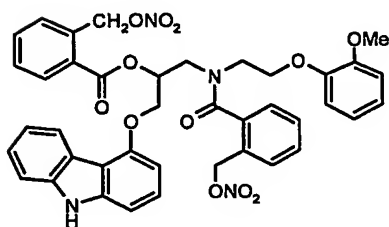
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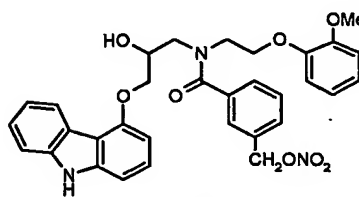
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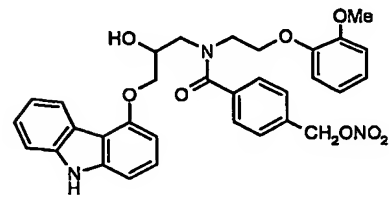
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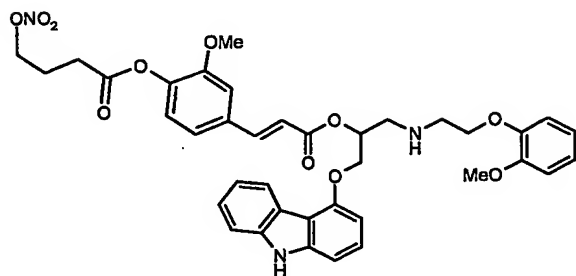
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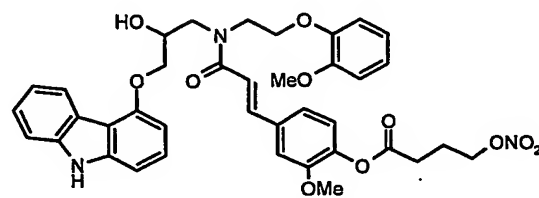
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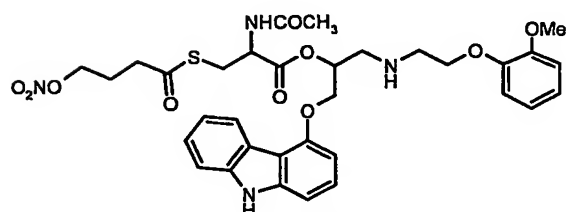
(15)



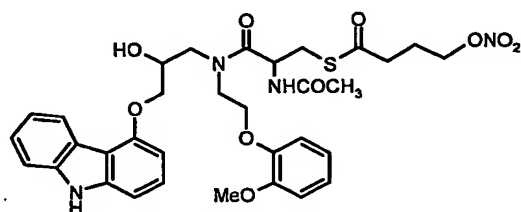
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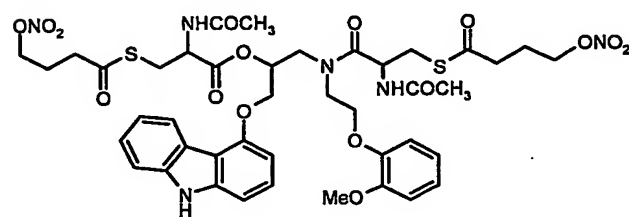
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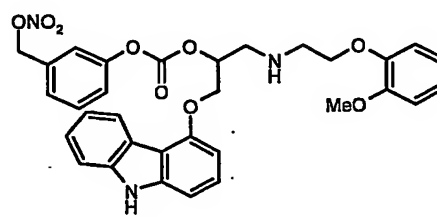
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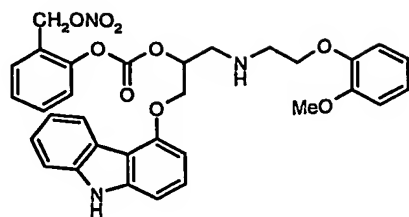
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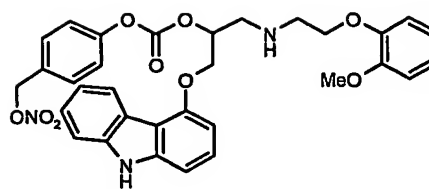
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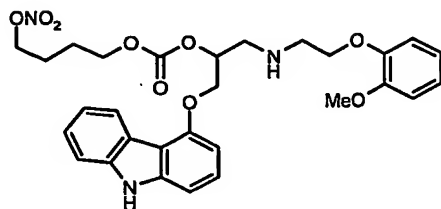
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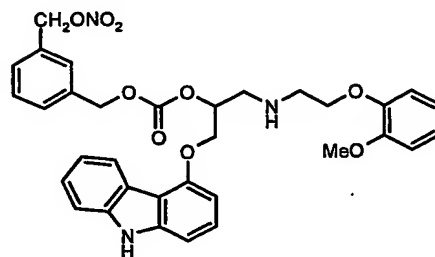
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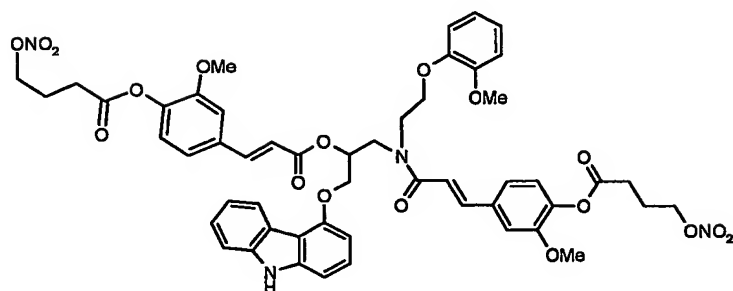
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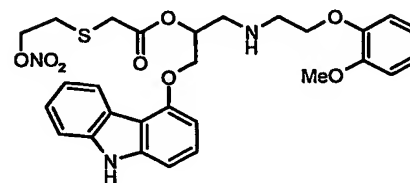
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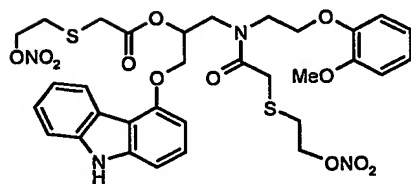
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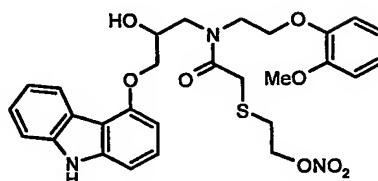
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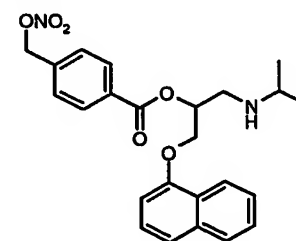
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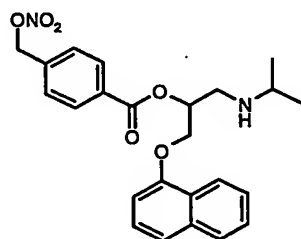
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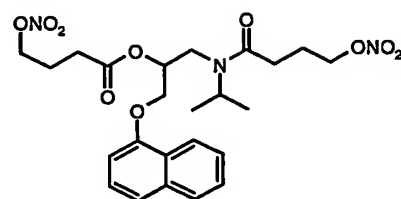
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(30)

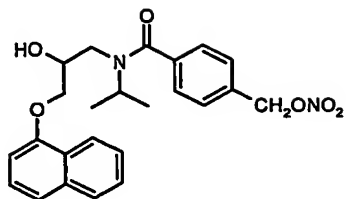


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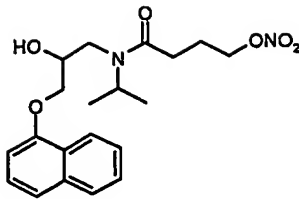


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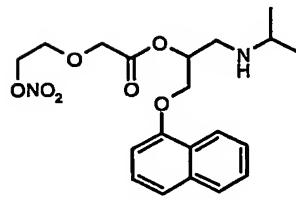
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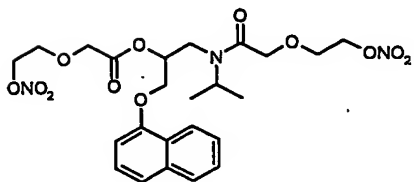
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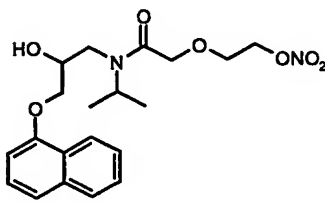
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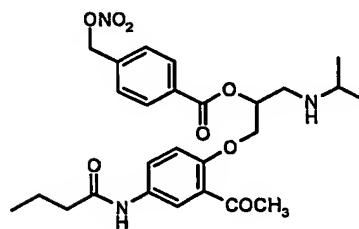
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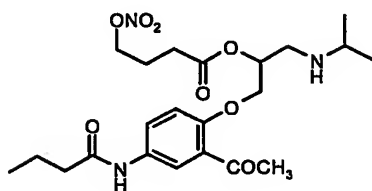
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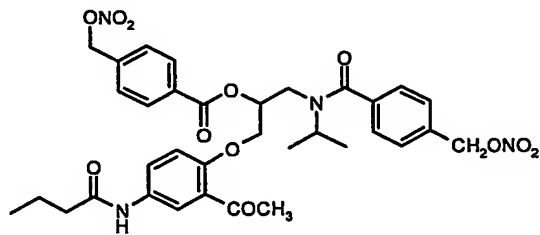
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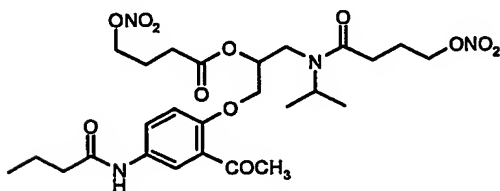
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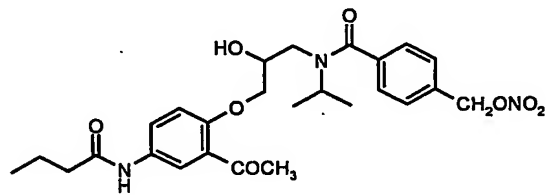
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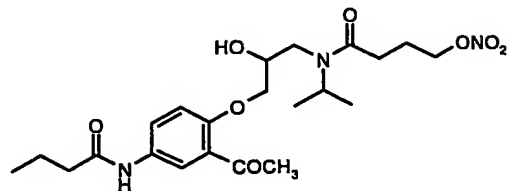
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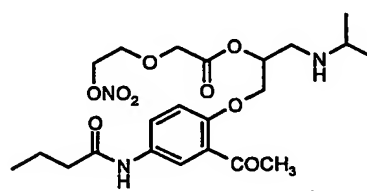
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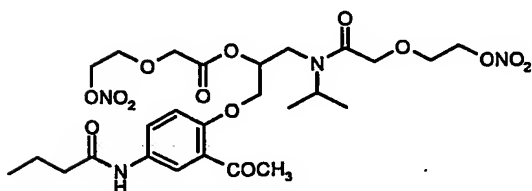
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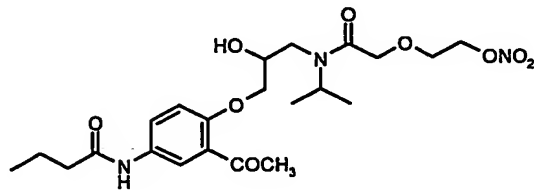
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(45)

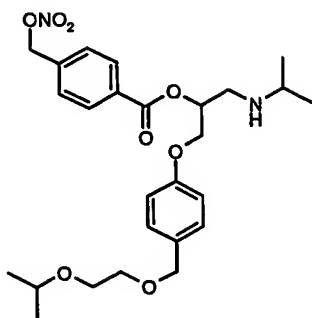


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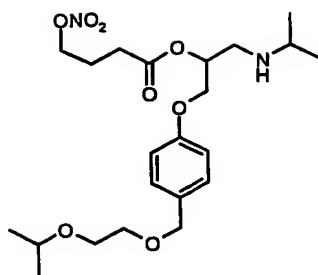


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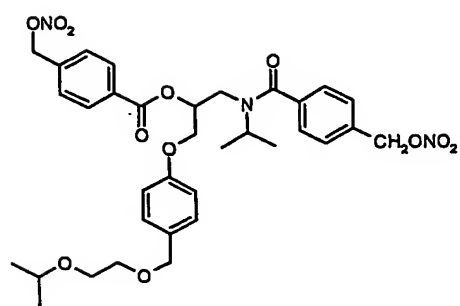
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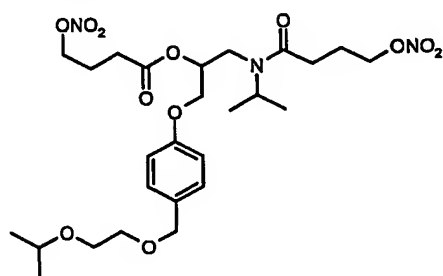
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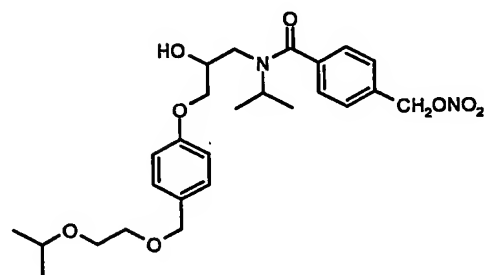
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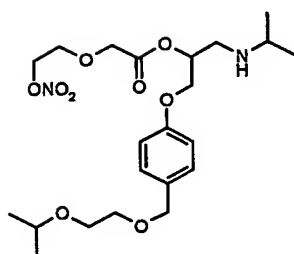
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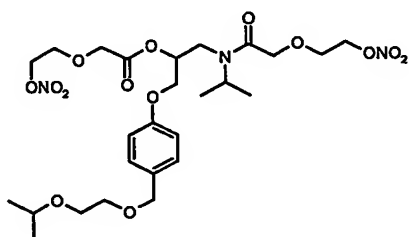
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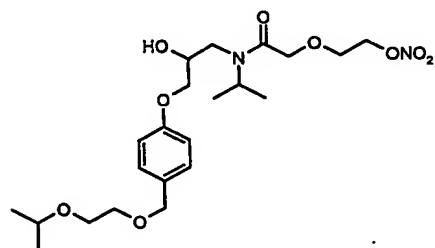
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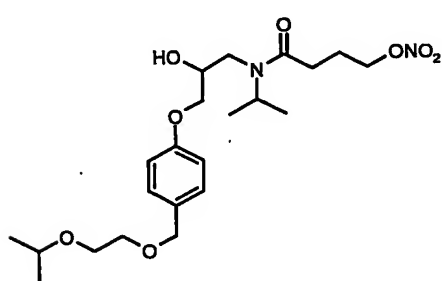
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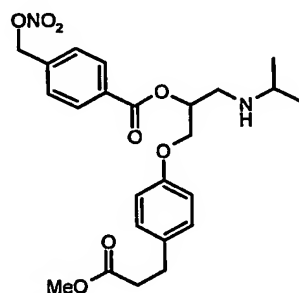
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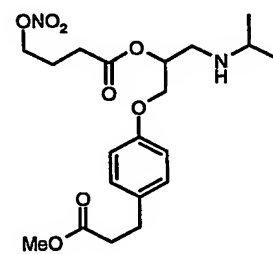
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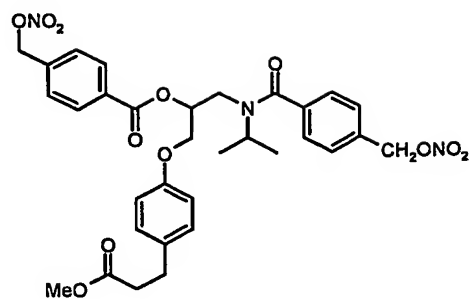
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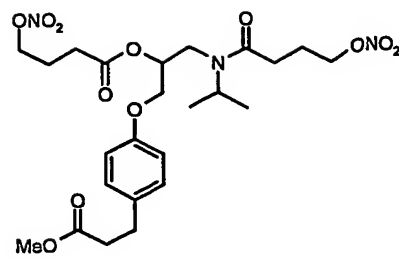
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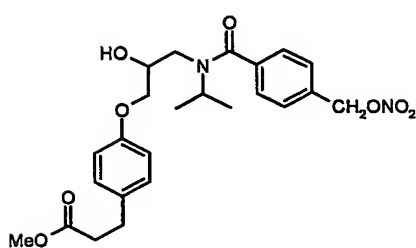
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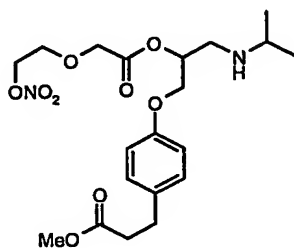
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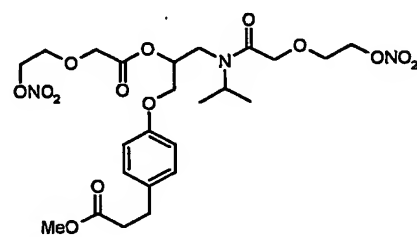
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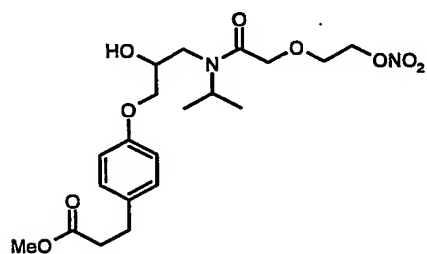
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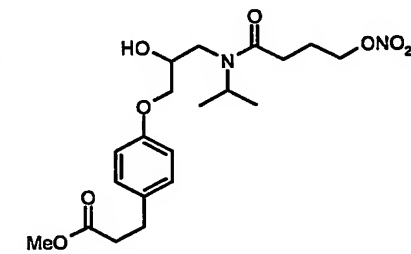
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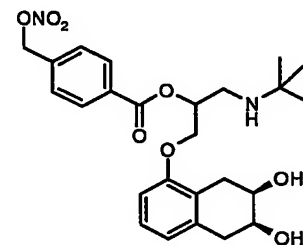
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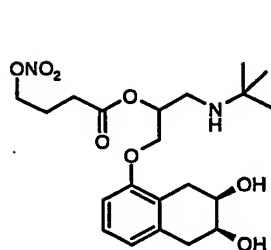
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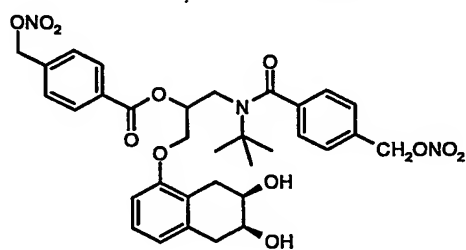
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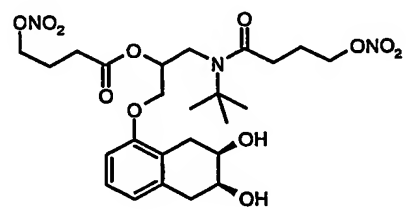
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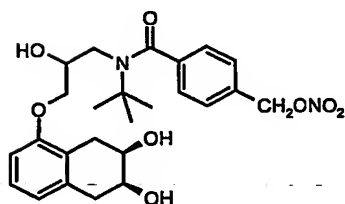
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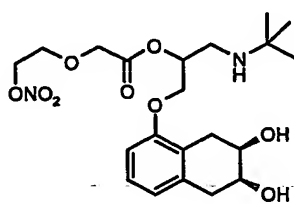
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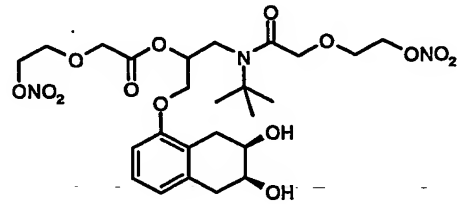
(69)



(70)

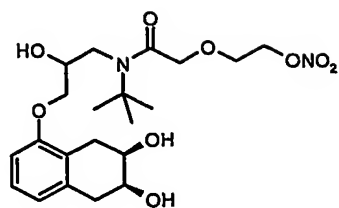


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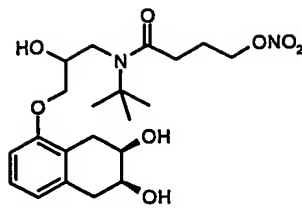


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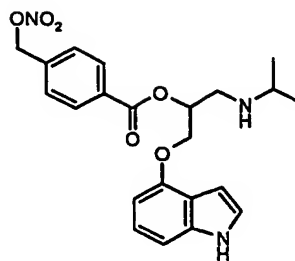
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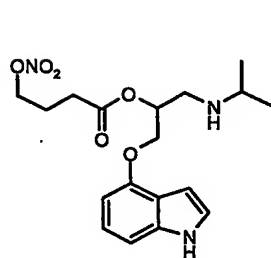
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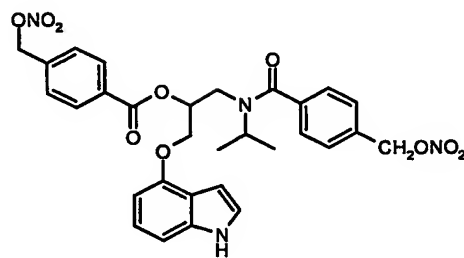
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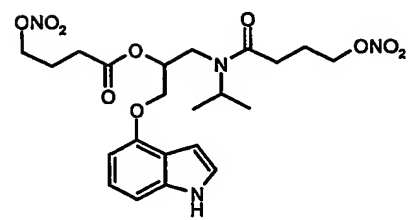
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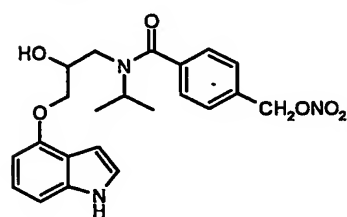
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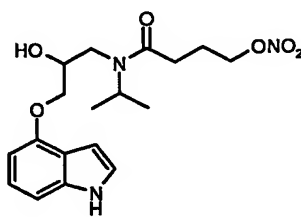
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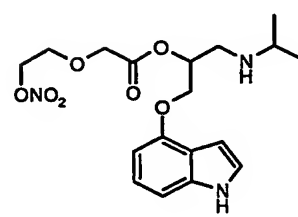
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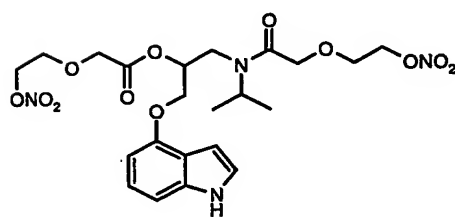
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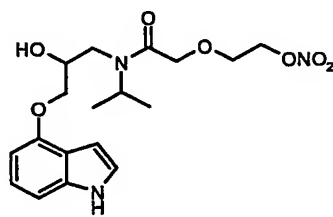
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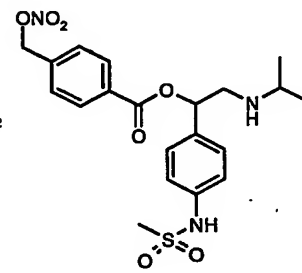
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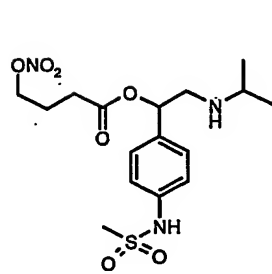
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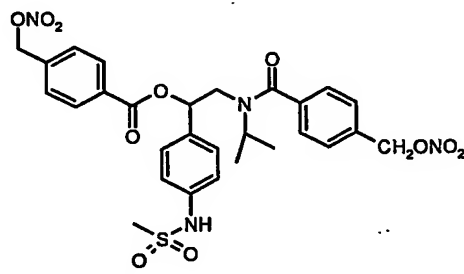
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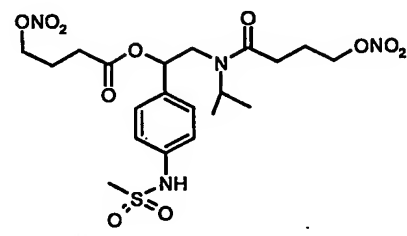
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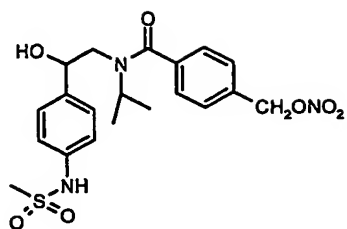


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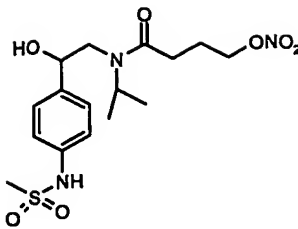
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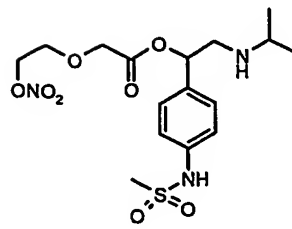
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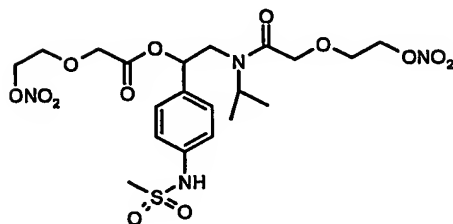
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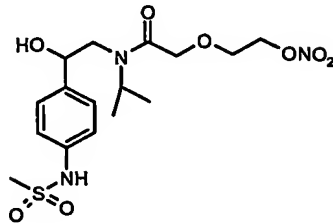
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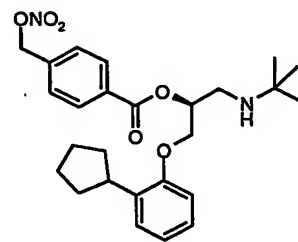
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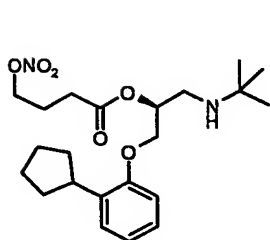
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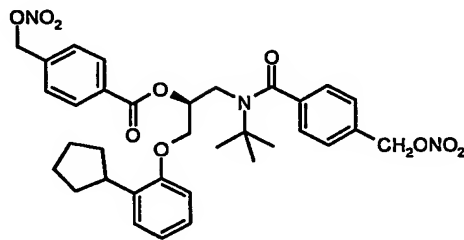
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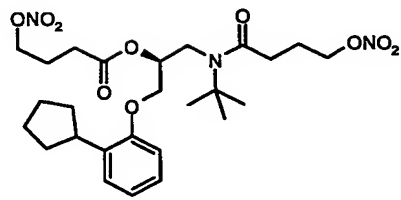
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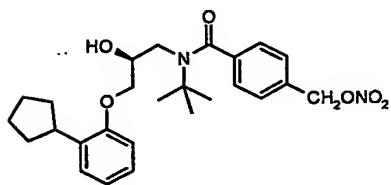
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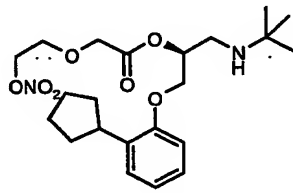
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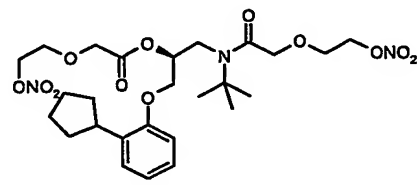
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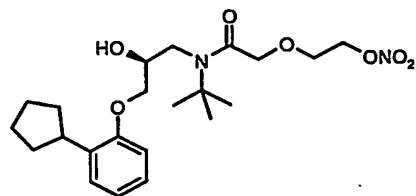
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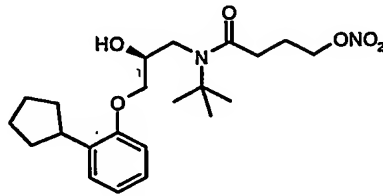
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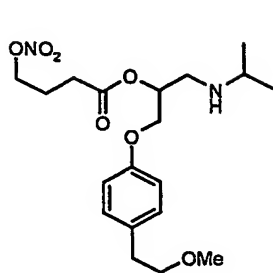
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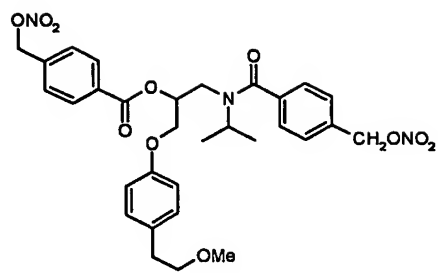
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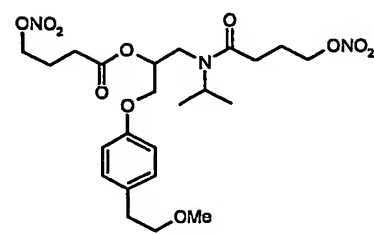
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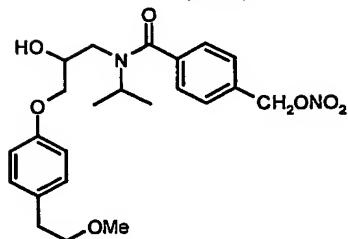
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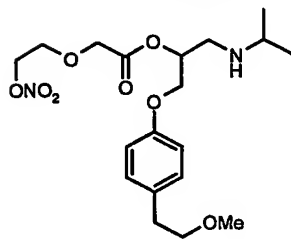
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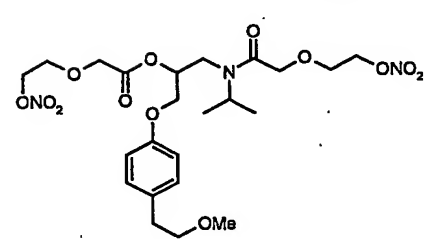
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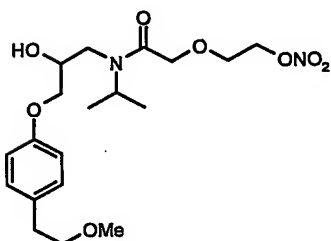
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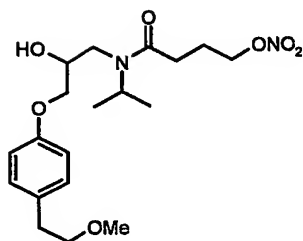
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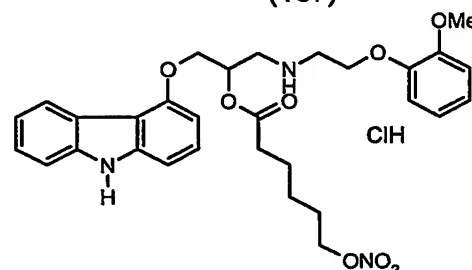
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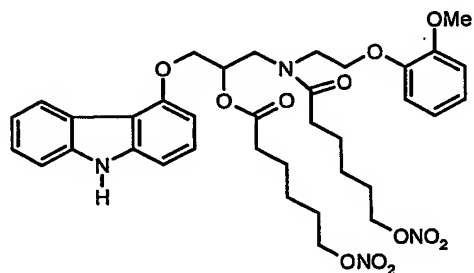
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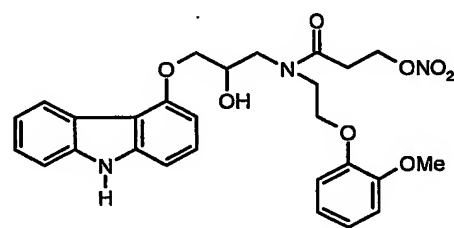
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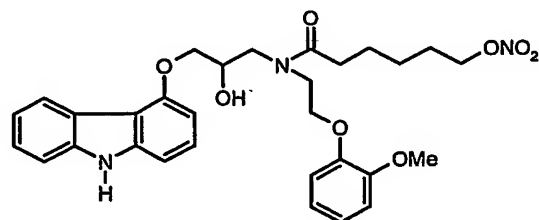
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Examples of "straight or branched C₁-C₂₀ alkylene" include, but are not limited to, methylene, ethylene, propylene, isopropylene, n-butylene, pentylene, n-hexylene and the like.

As stated above, the invention includes also the pharmaceutically acceptable salts
5 of the compounds of formula (I) and stereoisomers thereof.

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, triethylamine, dibenzylamine, piperidine and other acceptable organic amines.

10 The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in an organic solvent such as acetonitrile, tetrahydrofuran with the corresponding organic or inorganic acids.

Examples of pharmaceutical acceptable organic acids are: oxalic, tartaric, maleic,
15 succinic, citric acids. Examples of pharmaceutical acceptable inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids. Salts with nitric acid are preferred.

The compounds of the invention which have one or more asymmetric carbon atoms can exist as optically pure enantiomers, pure diastereomers, enantiomers mixtures, diastereomers mixtures, enantiomer racemic mixtures, racemates or racemate mixtures.
20 Within the object of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

The compounds and compositions of the present invention can be administered by any available and effective delivery system including but not limited to, orally, buccally, parenterally, by inhalation spray, by topical application, by injection, transdermally, or
25 rectally (e.g. by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Parenteral includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion technique.

Solid dosage forms for oral administration can include for example capsule,
30 tablets, pills, powders, granules and gel. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage form can also comprise, as normal practice, additional substance other than inert diluent, e.g., lubricating agent such as magnesium stearate.

Injectable preparations, for example sterile injectable aqueous or oleaginous
35 suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents.

The composition of this invention can further include conventional excipients, i.e., pharmaceutical acceptable organic or inorganic substances which do not deleteriously react with the active compounds.

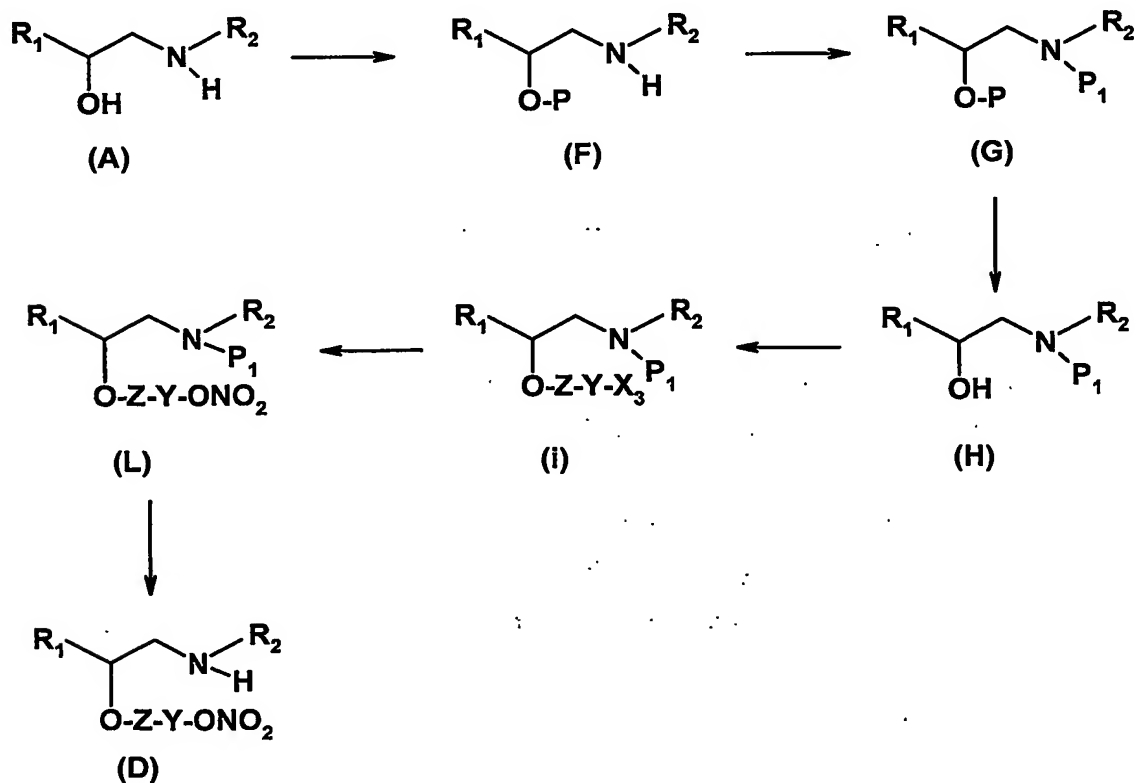
The doses of β -adrenergic blockers nitrooxyderivatives can be determined by standard clinique technique and are in the same ranges or less than as described for commercially available compounds as reported in the: Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 58th Ed., 2004; The pharmacological basis of therapeutics, Goodman and Gilman, J. G. Hardman, L. e. Limbird, 20th Ed.

EXPERIMENTAL

Synthesis procedure

Compounds of the invention can be synthesized as shown in Schemes 1 to 6. Compounds of general formula (I) $A-(Y-ONO_2)_s$, defined in Scheme 1-3 as compounds of formula D, wherein s is 1, Y is as above defined and A is a β -adrenergic blocker residue of formula (II), wherein Z is $-C(O)-$ and Z_1 is H, the enantiomers, diastereoisomer and a pharmaceutically acceptable salt thereof, can be prepared as outlined in Schemes 1 -3.

Scheme 1



Compounds of formula (i) wherein R_1 , R_2 , Z and Y are as above defined, P_1 is an amine protecting group such as tert-butyloxycarbonyl ester (t-Boc) and X_3 is an halogen atom

preferably Cl, Br and I, are converted to compounds of formula (L) wherein R_1 , R_2 , P_1 , Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofuran, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature to the boiling temperature of the solvent. The compounds of formula (L) are converted to the compounds of formula (D) by deprotecting the amine group (strong acid, such as HCl in dioxane or trifluoroacetic acid, is used to remove a t-butyl carbamate). Other preferred methods for removing the amine protecting groups are those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980.

- 10 The compounds of formula (H) wherein R_1 , R_2 , Z, P_1 and Y are as above defined, are converted to the esters of formula (i) wherein R_1 , R_2 , Y, Z, X_3 and P_1 are as above defined, by reaction with an appropriate acid (Q1) of formula X_3 -Y-COOH wherein Y and X_3 are as above defined. The reaction is generally carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from 0°C to 50°C in presence of a dehydrating agent such as dicyclohexylcarbodiimide DCC or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC HCl) with a catalyst, such as 4-N,N-dimethylaminopyridine (DMAP).

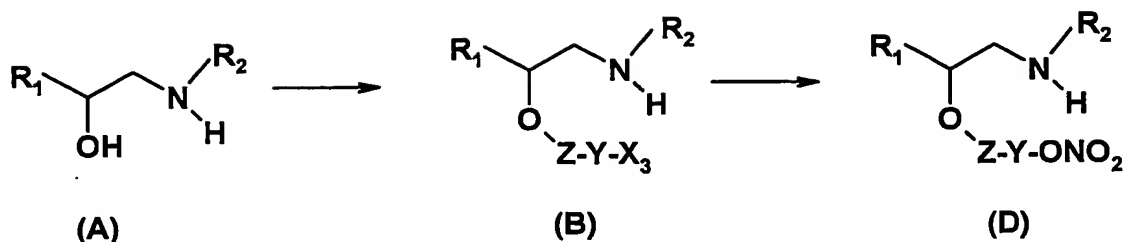
- 20 The compounds of formula (H) wherein R_1 , R_2 and P_1 are as above defined, can be obtained by deprotecting the hydroxylic group of the compounds of formula (G) wherein R_1 , R_2 are as above defined and P is a hydroxylic protecting group such as silyl ethers, such as trimethylsilyl or tert-butyl-dimethylsilyl and those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980. Fluoride ion is the preferred method for removing silyl ether protecting group.

- 25 The compounds of formula (G) wherein R_1 , R_2 , P and P_1 are as above defined, can be obtained by reacting the compounds of formula (F) wherein R_1 , R_2 and P are as above defined with a suitable amine protecting group (P_1) as above described.

- The alcohol group of the compounds of formula (A) wherein R_1 , R_2 are as above defined, is protected to afford the compounds of formula (F) wherein R_1 , R_2 are as above defined
- 30 Preferred protecting group for the alcohol moiety are silyl ethers, such as trimethylsilyl or tert-butyl-dimethylsilyl.

The compounds (A) wherein R_1 , R_2 are as above defined are commercially available, the acids of formula X_3 -Y-COOH wherein X_3 is as above defined, are commercially available.

40



Compounds of formula (B) wherein R_1 , R_2 , Z, Y are as above defined and X_3 is an halogen atom, such as Cl, Br and I, are converted to compounds of formula (D) wherein R_1 , R_2 , Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.

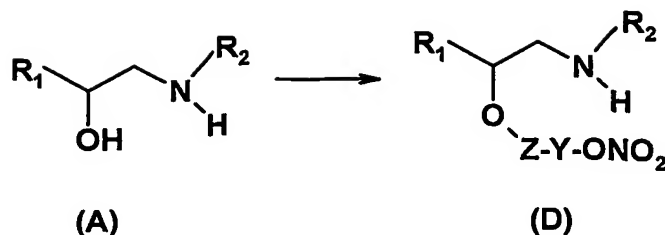
The compounds of formula (B) wherein R_1 , R_2 , Z, Y and X_3 are as above defined can be obtained by reaction of the compounds of formula (A) with an appropriate acyl chloride (Q) of formula $X_3-Y-C(O)Cl$, wherein X_3 is chosen among chlorine, bromine, and Y is as above defined. The esterification is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, chloroform in presence of a base as triethylamine, pyridine at a temperature from room temperature and 50°C. The reaction is completed within a time range from 30 minutes to 24 hours.

Alternatively the compounds of formula (B) can be obtained by reaction of compounds of formula (A) with an acid (Q1) of formula $X_3-Y-C(O)OH$ in the presence of a dehydrating agent as dicyclohexylcarbodiimide (DCC) or N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDAC) and a catalyst, such as N,N-dimethylamino pyridine. The reaction is carried out in an inert organic solvent such as as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from 0°C and 50°C. The reaction is completed within a time range from 30 minutes to 36 hours.

The compounds of formula (Q1), where X_3 is an halogen atom are commercially available or can be obtained from the corresponding commercially available hydroxy acid by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of P^{III} or P^V in solvents inert such as toluene, chloroform, DMF, etc.

The compounds (A) wherein R_1 , R_2 are as above defined are commercially available

Scheme 3

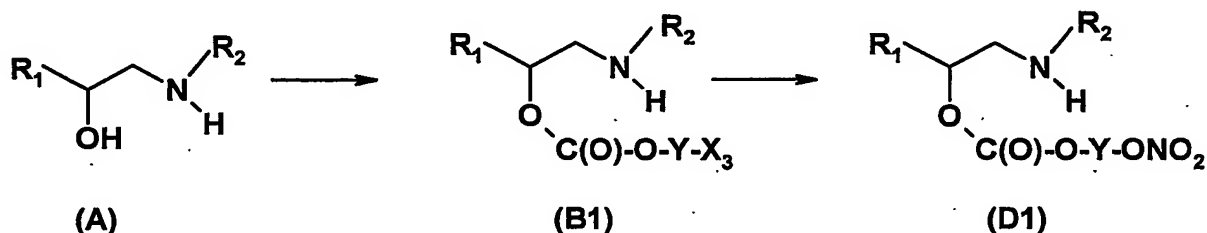


Alternatively the compounds of formula (D) can be obtained as described below. The compounds of formula are converted to the compounds (D) by reaction of hydroxy group with a nitrooxy derivative, containing activated acylating group, of formula $\text{Cl}(\text{O})\text{C}-\text{Y}-\text{ONO}_2$.

The nitrooxy compounds can be obtained from the corresponding alcohols of formula $\text{Cl}(\text{O})\text{C}-\text{Y}-\text{OH}$ by reaction with nitric acid and acetic anhydride in a temperature range from -50°C to 0°C or from the corresponding halogen derivatives of formula $\text{Cl}(\text{O})\text{C}-\text{Y}-\text{Hal}$ by reaction with silver nitrate in the presence of an inert solvent such as acetonitrile, tetrahydrofuran. A silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, a temperature from the boiling temperature and room temperature. The reaction is completed within a time range from 30 minutes to 3 days.

The compounds of general formula (I) $\text{A}-(\text{Y}-\text{ONO}_2)_s$, defined in Scheme 4 as compounds of formula (D1), wherein s is 1, Y is as above defined and A is a β -adrenergic blocker residue of formula (II), wherein Z is $-\text{C}(\text{O})\text{O}-$ and Z_1 is H , the enantiomers, diastereoisomer and a pharmaceutically acceptable salt thereof, can be prepared as outlined in Scheme 4.

Scheme 4

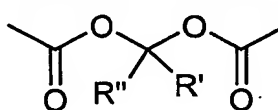


The compounds of formula (B1) wherein R_1 , R_2 , Y are as above defined and X_3 is a halogen atom, such as Cl , Br and I , are converted to compounds of formula (D1) wherein R_1 , R_2 , and Y are as above defined, by reaction with AgNO_3 in a suitable organic solvent such as acetonitrile, tetrahydrofuran, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.

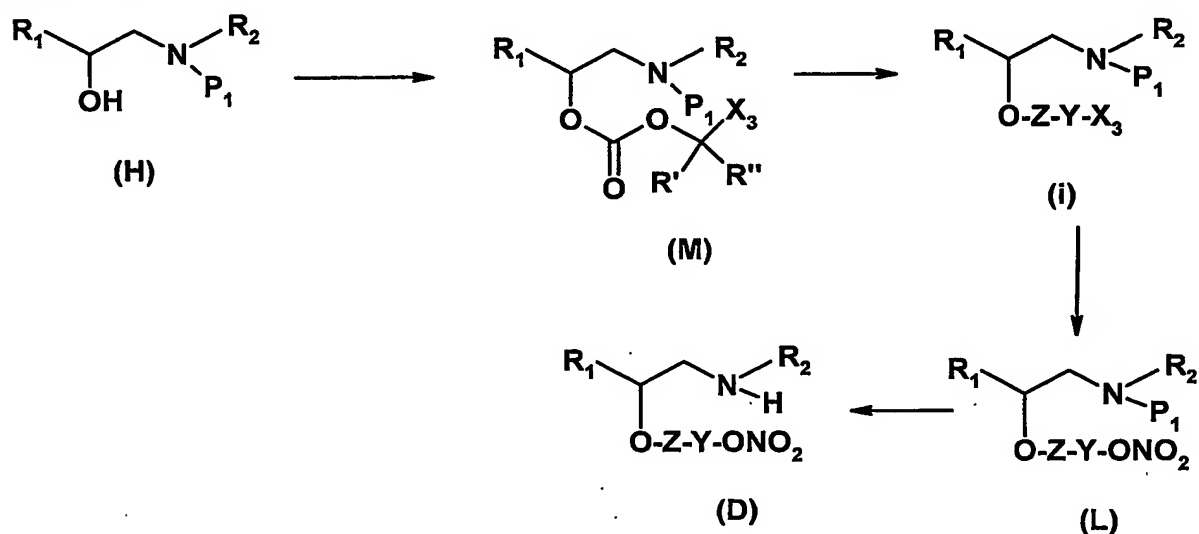
The compounds of formula (A) wherein R_1 and R_2 are as above defined are converted to the compounds (B1) by reaction with an appropriate compound (Q2) having formula $X_3-Y-OC(O)Cl$ wherein X_3 is Cl, Br or I, and Y is as defined above. The reaction is generally carried out in presence of a base in an aprotic polar or non-polar solvent such as THF or CH_2Cl_2 at temperature range between $0^\circ-65^\circ C$ or in a double phase system H_2O/Et_2O at temperature range between $20^\circ-40^\circ C$.

The compounds of formula (Q2) are commercially available or can be obtained from the corresponding alcohols by reaction with triphosgene in presence of an organic base.

The compounds of general formula (I) $A-(Y-ONO_2)_s$, defined in Scheme 5 as compounds of formula (D), wherein s is 1, Y is as above defined and A is a β -adrenergic

blocker residue of formula (II), wherein Z is  wherein R' and R'' are H or straight or branched C_1-C_4 alkyl and Z_1 is H, the enantiomers, diastereoisomer and a pharmaceutically acceptable salts thereof, may be prepared as outlined in Scheme 5:

Scheme 5



The compounds of formula (i) wherein R_1 , R_2 , Z and Y are as above defined, P_1 is an amine protecting group such as tert-butyloxycarbonyl ester (t-Boc) and X_3 is an halogen atom such as Cl, Br and I, are converted to compounds of formula (L) wherein R_1 , R_2 , P_1 , Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofurane, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent. The compounds of formula (L) are converted to the compounds of formula (D) by deprotecting the amine group (strong acid, such as HCl in

dioxane or trifluoroacetic acid, is used to remove a t-butyl carbamate). Other preferred methods for removing the amine protecting groups are those described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980.

The compounds of formula (i) wherein R_1 , R_2 , Y , X_3 , Z and P_1 are as above defined, can be obtained by reacting the compounds of formula (M) wherein R_1 , R_2 , P_1 , R' , R'' and X_3 are as above defined, with an acid (Q1) of formula X_3 -Y-COOH wherein X_3 is an halogen atom and Y is as above defined. The reaction is carried out in an inert organic solvent such as N,N'-dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature range from 0°C and 50°C in the presence of a dehydrating agent such as dicyclohexylcarbodiimide DCC or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC HCl) with a catalyst, such as 4-N,N-dimethylaminopyridine (DMAP).

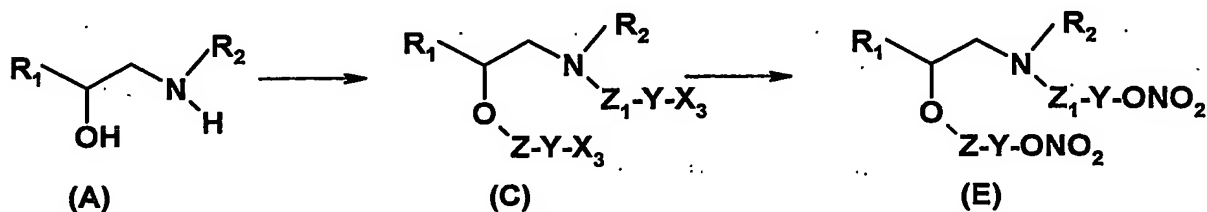
The reaction is complete within a time ranges from 30 minutes to 24 hours.

The compounds of formula (M) wherein R_1 , R_2 , P_1 , R' , R'' and X_3 are as above defined, can be obtained by reacting the compounds the of formula (H) with a compound (S) of formula X_3 -C(R')(R'')-OC(O) X_3 wherein X_3 is an halogen atom. The reaction is carried out in presence of an organic or inorganic base in a polar solvent as DMF, THF, acetonitrile at a temperature in the range from -5°C to 60°C or in a double phase system according to methods well known in the literature.

The amine group of the compounds (A) is protected to afford the compounds of formula (H) wherein P_1 is a suitable amine protecting group such as tert-butyloxycarbonyl ester (t-Boc) The compounds (S) are commercially available.

The compounds of general formula (I) A -(Y-ONO₂)_s, defined in Scheme 6 as compounds of formula (E), wherein s is 2, Y is as above defined and A is a β -adrenergic blocker residue of formula (II), wherein Z_1 and Z are -C(O)-, the enantiomers, diastereoisomer and a pharmaceutically acceptable salt thereof, can be synthesized as shown in Scheme 6.

Scheme 6



Compounds of formula (C) wherein R_1 , R_2 , Z , Z_1 and Y are as above defined and X_3 is an halogen atom, such as Cl, Br and I, are converted to compounds of formula (E) wherein

R_1 , R_2 , Z and Y are as above defined, by reaction with $AgNO_3$ in a suitable organic solvent such as acetonitrile, tetrahydrofuran, a silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, at a temperature from room temperature and the boiling temperature of the solvent.

- 5 The compounds of formula (C) wherein R_1 , R_2 , Z , Z_1 , Y and X_3 are as above defined can be obtained by reaction of the compounds of formula (A) with an appropriate acyl halide (Q) of formula $X_3-Y-C(O)Cl$, wherein X_3 is chosen among chlorine, bromine, and Y is as above defined. The reaction is carried out in an inert organic solvent such as N,N' -dimethylformamide, tetrahydrofuran, benzene, toluene, chloroform in presence of a base as triethylamine, pyridine at a temperature from room temperature and $50^\circ C$. The reaction is completed within a time range from 30 minutes to 24 hours.

- 10 Alternatively the compounds of formula (C) can be obtained by reaction of the compounds of formula (A) with an acid (Q1) of formula $X_3-Y-COOH$ in the presence of a dehydrating agent such as dicyclohexylcarbodiimide (DCC) or $N'-(3\text{-dimethylaminopropyl})\text{-}N$ -ethylcarbodiimide hydrochloride (EDAC) and a catalytic amount of N,N -dimethylamino pyridine. The reaction is carried out in an inert organic solvent such as N,N' -dimethylformamide, tetrahydrofuran, benzene, toluene, dioxane, a polyhalogenated aliphatic hydrocarbon at a temperature from $0^\circ C$ and $50^\circ C$. The reaction is completed within a time range from 30 minutes to 36 hours.

- 15 20 The compounds of formula (Q1), where X_3 is an halogen atom are commercially available or can be obtained from the corresponding commercially available hydroxy acid by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of P^{III} or P^V in solvents inert such as toluene, chloroform, DMF, etc.

The compounds (A) wherein R_1 , R_2 are as above defined are commercially available.

- 25 The compounds of formula (E) can also be obtained as described below. The compounds of formula A are converted to the compounds (E) by reaction with a nitrooxy derivative of formula $Cl(O)C-Y-ONO_2$ containing an activated acylating group.

- The nitrooxycompounds can be obtained from the corresponding alcohols of formula $Cl(O)C-Y-OH$ by reaction with nitric acid and acetic anhydride in a temperature range from $-50^\circ C$ to $0^\circ C$ or from the corresponding halogen derivatives of formula $Cl(O)C-Y-Hal$ by reaction with silver nitrate in the presence of an inert solvent such as acetonitrile, tetrahydrofuran. A silver nitrate molar excess is preferably used and the reaction is carried out, in the dark, a temperature from the boiling temperature and room temperature. The reaction is completed within a time range from 30 minutes to 3 days.

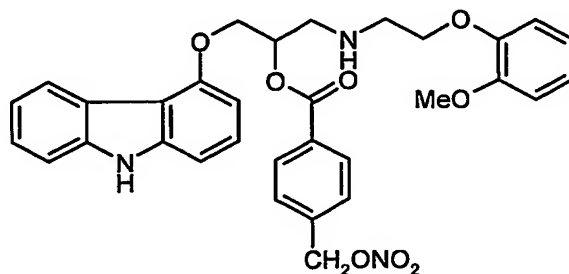
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Examples

The following non-limiting examples further describe and enable one of ordinary skilled in the art to make and use the present invention.

Example 1

- 5 4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl] amino]-2-propanoate of formula (8).



(8)

- 10 **1a.** 4-(Chloromethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl] amino]-2-propanoate

To a solution of carvedilol (2g, 5mmol) in chloroform (50ml) 4-chloromethyl benzoic acid (0.9g, 5.5mmol), EDAC (1.15g, 6mmol) and N,N-dimethylaminopyridine (catalytic amount) were added. The reaction was stirred at room temperature for 24 hours. The solution was treated with water and the organic layer was dried over sodium sulphate. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 6/4 ($R_f=0.2$). The title product 0.27g was obtained as a white powder.

- 15 **1b.** 4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl] amino]-2-propanoate

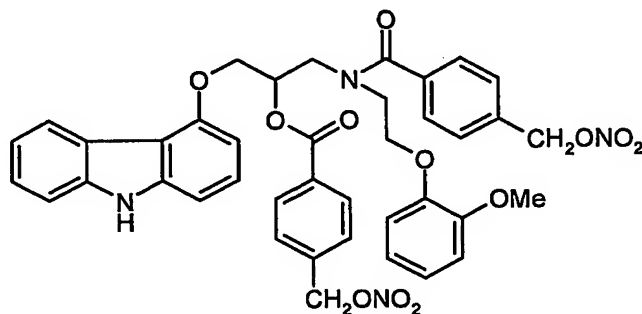
20 A solution of the product of Example 1a (0.27g, 0.48mmol) and silver nitrate (0.16g, 0.96mmol) in acetonitrile (30ml) was stirred at 60°C, in the dark, for 36 hours. The precipitated (silver salts) was filtered off and the solvent was evaporated under vacuum. The residue was treated with chloroform and water. The organic layer was dried over sodium sulphate. The solvent was evaporated and the residue was purified by flash chromatography eluting with ethyl acetate/n-hexane 6/4. The title product 0.03g was obtained as a white powder.

25 $^1\text{H-NMR}$ (DMSO) δ (ppm): 11.31 (1H,s); 8.15 (2H,m); 7.8-7.5 (2H,m); 7.43 (1H,d); 7.30 (2H,m); 7.15-6.85 (7H,m); 6.77 (1H,d); 6.03 (1H,m); 5.65 (2H,s); 4.55 (2H,m); 4.33 (2H,m); 4.0-3.7 (5H,m); 3.51 (2H,m).

30

Example 2

4-(Nitrooxymethyl)benzoic acid 1- (9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-nitrooxymethyl)benzoyl] amino]-2-propanoate of formula (11).



(11)

5 **2a.** 4-(Chloromethyl)benzoic acid 1- (9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-chloromethyl)benzoyl] amino]-2-propanoate

To a solution of carvedilol (2g, 5mmol) in chloroform (50ml) 4-chloromethyl benzoic acid (0.9g, 5.5mmol), EDAC (1.15g, 6mmol) and N,N-dimethylaminopyridine (catalytic amount) were added. The reaction was stirred for 24 hours at room temperature. The solution was treated with water and the organic layer was dried over sodium sulfate and filtered. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 1/1 (R_f=0.42). The title product (0.06g) was obtained as a white powder.

15 **2b.** 4-(Nitrooxymethyl)benzoic acid 1- (9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-nitrooxymethyl)benzoyl] amino]-2-propanoate

A solution of the product of example 2a (0.06g, 0.08mmol) and silver nitrate (0.06g, 0.32mmol) in acetonitrile (20ml) was stirred at 60°C, in the dark, for 36 hours. The precipitated (silver salts) was removed by filtration. The filtrate was concentrated and the residue was treated with chloroform and water. The combined organic layer extracts were dried over sodium sulfate and filtered. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 6/4. The title product 0.015g was obtained as a powder.

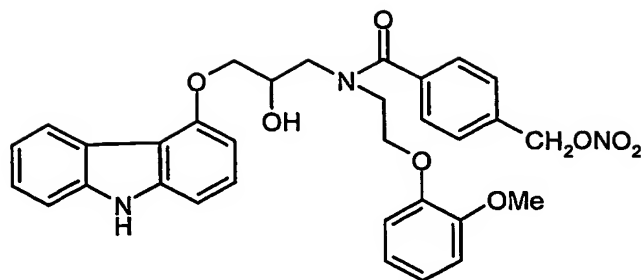
¹H-NMR (DMSO) δ (ppm): 1.24(1H,s); 8.1 (3H,m); 7.7-7.2 (8H,m); 7.2-6.7 (8H,m); 6.05 (1H,m); 5.6-5.8 (4H,d); 4.55 (1H,m); 4.30 (2H,m); 4.15 (3H,m); 3.71 (5H,s).

25

Example 3

1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-nitrooxymethyl)benzoyl] amino]-2-propanol of formula (15)

47



(15)

3a. 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-chloromethyl)benzoyl]amino]-2-propanol

5 To a solution of carvedilol (2g, 5mmol) in chloroform (50ml) 4-chloromethyl benzoic acid (0.9g, 5.5mmol), EDAC (1.15g, 6mmol) and N,N-dimethylaminopyridine (catalytic amount) were added. The reaction was stirred for 24 hours at room temperature. The solution was treated with water and the organic layer was dried over sodium sulfate and filtered. The solvent was evaporated and the residue was purified by flash
10 chromatography eluting with n-hexane/ethyl acetate 6/4 (R_f=0.42). The title product 1.05g was obtained as a white powder.

3b. 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-nitrooxymethyl)benzoyl]amino]-2-propanol

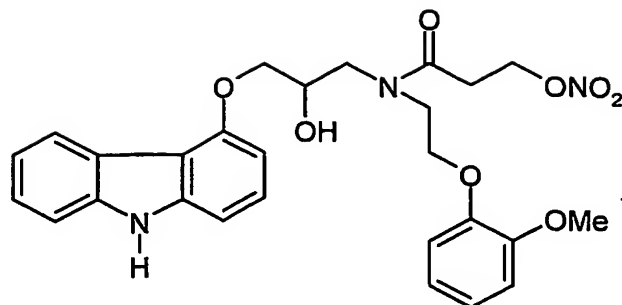
A solution of the product of example 3a (1.0g, 1.78mmol) and silver nitrate (0.6g, 3.6 mmol) in acetonitrile (100ml) was stirred at 65°C, in the dark, for 32 hours. The precipitated (silver salts) was removed by filtration. The filtrate was concentrated and the residue was treated with methylene chloride and water. The combined organic layer
15 extracts were dried over sodium sulphate. The solvent was evaporated and the residue was purified by flash chromatography eluting with n-hexane/ethyl acetate 1/1. The title product 0.4g was obtained as yellow powder.

¹H-NMR (DMSO) δ (ppm): 11.24 (1H,s); 8.40-6.50 (15H,m); 5.61 (2H,m); 5.51 (1H,m); 5.36 (1H,m); 4.40-3.90 (4H,m); 3.74-3.71 (7H,m).

Example 4

25 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(3-nitrooxypropanoyl)amino]-2-propanol of formula (112)

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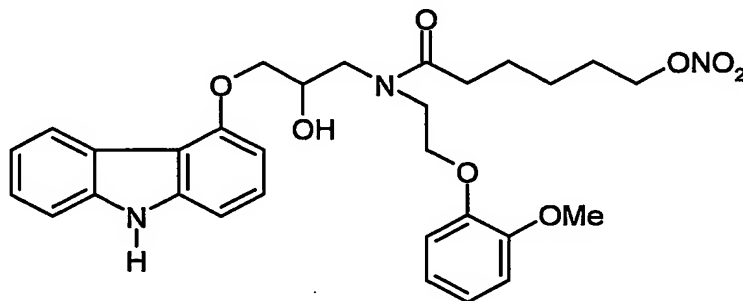
The compound was synthesized under the analogous procedure described in example 3 starting from carvedilol and 3-bromopropanoic acid.

¹H-NMR (DMSO) δ (ppm): 11.24 (1H, s); 8.25 (1H, dd); 7.46 (1H, dd); 7.29 (2H, m); 7.08 (2H, m); 6.90 (4H, m); 6.70 (1H, dd); 5.50 (1H, d); 4.80 (2H, m); 4.35 (1H, m); 4.20-3.6(9H, m); 3.6-2.8 (4H, m).

Example 5

1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(6-nitrooxyhexanoyl)amino]-2-propanol of formula (113)

10



The compound was synthesized under the analogous procedure described in example 3 starting from carvedilol and 6-bromohexanoic acid.

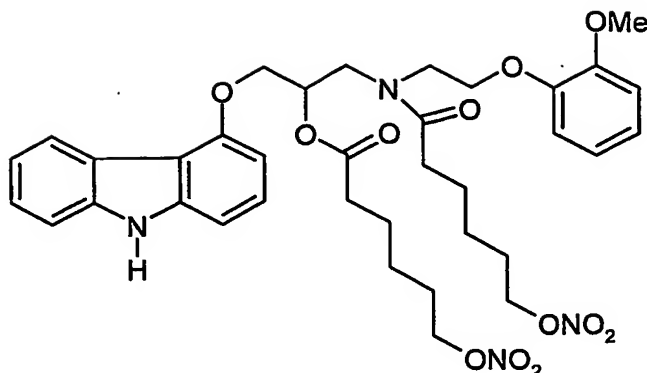
¹H-NMR (DMSO) δ (ppm): 11.24 (1H, s); 8.25 (1H, dd); 7.46 (1H, dd); 7.29 (2H, m); 7.08 (2H, m); 6.90 (4H, m); 6.70 (1H, dd); 5.40 (1H, d); 4.50 -3.50 (13H, m); 2.6-2.3 (2H, m); 1.70-0.50 (6H, m).

Example 6

6-(nitrooxy)hexanoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl]-[(6-nitrooxyhexanoyl] amino]-2-propanol of formula (111)

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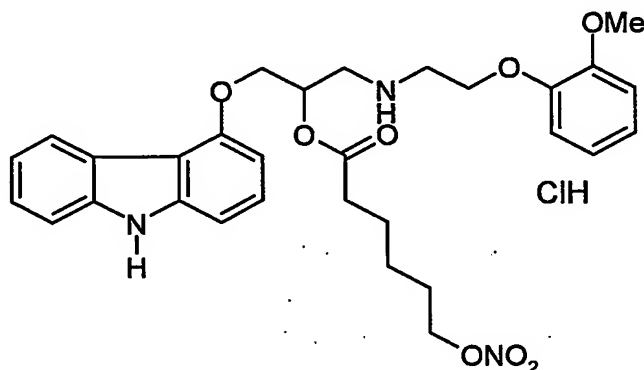


The compound was synthesized under the analogous procedure described in example 2 starting from carvedilol and 6-bromohexanoic acid.

¹H-NMR (DMSO) δ (ppm): 11.24 (1H, s); 8.15 (1H, dd); 7.46 (1H, dd); 7.29 (2H, m); 7.08 (2H, m); 6.90 (4H, m); 6.70 (1H, dd); 5.65 (1H, m); 4.6-4.20 (6H, m); 4.2-3.5 (9H, m); 2.50 (2H, m); 2.29 (2H, m); 1.70-0.60 (12H, m).

Example 7

10 6-(nitrooxy)hexanoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl]amino]-2-propanol hydrochloride of formula (110)



15 The compound was synthesized under the analogous procedure described in example 1 starting from carvedilol and 6-bromohexanoic acid.

¹H-NMR (DMSO) δ (ppm): 11.30(1H, s); 8.15 (1H, dd); 7.44 (1H, dd); 7.32 (2H, m); 7.10-6.90 (6H, m); 6.70 (1H, dd); 5.65 (1H, m); 4.50-4.20 (7H, m); 3.90-3.40 (7H, m); 2.40 (2H, m); 1.60-1.10 (6H, m).

20

Example 8

Measurements of cGMP in rat PC12 cell line.

cGMP contributes to the function and interaction of several vascular cell types and its dysfunction is involved in major cardiovascular diseases such as hypertension, diabetic complications, atherosclerosis, and tissue infarction. Therefore the extent of cGMP formation elicited by the compounds of the inventions was evaluated in the rat pheochromocytoma (PC12) cell line.

Tested compounds

1) Carvedilol (parent drug)

2) 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(4-nitrooxymethyl)benzoyl]amino]-2-propanol (compound of example 3);

3) 4-(Nitrooxymethyl)benzoic acid 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanoate (compound of example 1);

4) 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(3-nitrooxypropanoyl)amino]-2-propanol (compound of example 4);

5) 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl][(6-nitrooxyhexanoyl)amino]-2-propanol (compound of example 5).

Method

Cells were maintained at 37°C in DMEM medium enriched with 10% horse serum and 5% foetal bovine serum under 5% CO₂ atmosphere. At the time of experiments the cells were washed once with Hank's Balanced Salt Solution (HBSS) supplemented with 0.05% ascorbic acid and preincubated in the same buffer for 10 min in a floating water bath. After the preincubation step, cells were exposed for additional 45 min to either control conditions or increasing concentrations of test compounds ranging from 0.1 to 25 µM, in the presence of the phosphodiesterase inhibitor, IBMX (100 µM) and the NO-independent activator of soluble guanylyl cyclase, YC-1 (20 µM). The reaction was terminated by the removal of the incubating buffer and consecutive addition of 100 µl of absolute ethanol. The organic extracts were then evaporated to dryness and the residues dissolved in aqueous buffer for quantitative determination of intracellular cGMP levels using the cGMP enzyme immunoassay kit.

The obtained results reported in Table 1 are expressed as EC₅₀ (µM) and efficacy E_{max} (% of vehicle). As shown in the table the nitroderivatives of carvedilol induced a consistent increase of intracellular cGMP formation in PC12 cell line. Conversely, this effect was not induced by the parent compound.

Table 1: Effects of the nitroxyderivatives of carvedilol and the carvedilol on cGMP accumulation in PC12 cells

Compound	EC ₅₀ (μM)	E _{max} (% of vehicle)
Carvedilol	Not effective	Not effective
Compound of example 3	1.8	565
Compound of example 1	2.3	480
Compound of example 4	1.7	395
Compound of example 5	0.6	322